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Drinking Water Criteria Document for Cadmium (Final Draft)

Life Systems, Inc., Cleveland, OH

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on cadmium.
This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of cadmium
- Toxicokinetics and human exposure to cadmium
- Health Effects of cadmium in humans and animals
- Mechanisms of toxicity of cadmium
- Quantification of toxicological effects of cadmium

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ICAIR
LIFE SYSTEMS, INC.
Cleveland, OH 44122

for

Criteria and Standards Division
Office of Drinking Water
U. S. Environmental Protection Agency
Washington, DC 20460

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I. SUMMARY

Cadmium (Cd) is an element of the transition metal series which occurs widely in nature, usually in lead or zinc ores. Elemental cadmium is insoluble in water, but many cadmium salts are quite soluble. Cadmium is manufactured primarily by roasting, and has widespread industrial use. In 1974, over 5,600 metric tons of cadmium were used in the United States for industrial and manufacturing operations. At present, little recycling of cadmium products occurs.

Following oral exposure, cadmium salts are not readily absorbed from the gastrointestinal tract in mice, rats, monkeys and humans. The extent of this absorption is influenced by diet and other factors. Measurements of whole-body retention of orally administered radiolabelled cadmium are used to estimate absorption in humans and animals, but this is correct only if retention in the gastrointestinal tract and enteric or biliary secretion can be neglected. Humans exposed to a drink containing radiolabelled cadmium chloride had an average body retention of 4.6% ± 4.0% (SD) with a range of 0.7% to 15.6% of the administered dose at the time when unabsorbed radioactivity was eliminated from the gastrointestinal tract (about one to five weeks post-exposure). Rice containing metabolized radiocadmium was fed to an adult human and the total body burden was 4.4% of the administered dose at six days post-exposure. The gastrointestinal absorption (expressed as whole body retention in percent of administered dose) in mice ranged from 0.5% to 3.2% at five days post-exposure. Approximately 2.3% of the cadmium chloride administered to rats was retained at four days post-exposure. Monkeys retained 2.5% to 3.2% (average 2.9%) of radiocadmium chloride administered by gavage at ten days post-exposure. Thus, retention studies demonstrate that cadmium absorption in animal species and humans typically ranges from about 1% to 5% with considerable individual variation and potential error due to the retention of unabsorbed cadmium in the gastrointestinal tract. Factors influencing absorption include age, sex, pregnancy and the dietary content of protein, Ca^{2+}, Zn^{2+} and other metals. In rats, cadmium salts are readily absorbed (41%) from the lung following inhalation. It has been estimated that 64% to 96% of cadmium from cigarette smoke deposited in the lung of humans is absorbed.

Absorbed cadmium is distributed to tissues throughout the body, with preferential accumulation in the liver and kidney. Concentrations in these tissues are often 10 to 100 times those in other tissues. Thus, from 60% to 80% of the absorbed dose will be found in the liver and kidney. In normal humans (not exposed to elevated concentrations of cadmium) in Japan, typical cadmium concentrations in tissues (µg Cd/g tissue) are: liver = 3 to 8, kidney = 36 to 58, other tissues = 0.1 to 1.2. The typical total body burden of cadmium in adult humans is about 35 mg, 33% of which is found in kidney and 24% in liver.

Cadmium is not metabolized by the body, but its absorption and distribution are influenced by metallothionein, a low molecular weight protein found in blood and tissues. The function of the protein is not certain, but it probably serves a protective role by chelating cadmium (and other metals). The ingestion of cadmium induces the synthesis of this protein. Thus, prior cadmium exposure influences cadmium toxicity, and urinary metallothionein may be a useful indicator of cadmium exposure.

Absorbed cadmium is excreted from the body primarily in the urine. The rate of excretion is very low (0.01% to 1% of total body burden per day), and half-lives of 50 to 500 days are reported for various animal species. A half-life of 10 to 38 years has been estimated in humans.

Because cadmium is excreted slowly, it steadily accumulates in body tissues, especially liver and kidney. A slow but continual accumulation in humans occurs throughout life. In animals or humans exposed to elevated levels of cadmium, there is increased and rapid deposition of cadmium in the liver, kidney and other tissues.

The principal routes of cadmium exposure in humans are drinking water, food and air. The limited data indicate that most (over 90%) of the approximately 214 million people in the Unites States using public water supplies are supplied with water containing cadmium concentrations of 2 µg/L or less. Approximately 60,000 people receive drinking water with cadmium levels above 10 µg/L. Cadmium intake from the diet is estimated to be about 33 µg/day. Intake of cadmium from the air is estimated at approximately 0.16 µg/day. The very limited data suggest that for individuals exposed to drinking water with cadmium levels less than 10 µg/L, the predominant source of cadmium is food, accounting for about 60% of the total daily intake. Drinking water significantly exceeds food as the predominant source of cadmium only at concentrations of 20 µg/L or more.

Cadmium is not considered to be essential for health of mammals. In rats, oral LD_{50} values for cadmium compounds range from 16 to more than 5,000 mg/kg.

Chronic oral ingestion of lower cadmium doses leads to injury of many tissues. Rats administered drinking water containing 25 to 300 mg Cd/L (about 2 to 25 mg Cd/kg/day) for several months or longer developed a variety of signs of renal damage, including proteinuria, aminoaciduria and abnormal histological appearance of proximal tubule cells. This was accompanied by increased cadmium content in the renal cortex, up to 230 µg/g tissue. Rats administered drinking water containing 10 mg Cd/L (about 1 mg Cd/kg/day) for six weeks did not develop significant proteinuria.

The livers of rats and rabbits ingesting water containing 17 to 160 mg Cd/L (about 1.5 to 15 mg Cd/kg/day) for 200 to 300 days were also observed to have histological signs of injury, although usual tests of liver function were normal. Hepatic tissue was generally devoid of glycogen and had varying degrees of collagen deposition in periportal and interlobular regions. A marked increase in smooth endoplasmic reticulum and dilatation of rough endoplasmic reticulum in the perilobular and periportal areas were also observed.

Osteomalacia occurred in female rats fed chow containing 100 µg Cd/g (about 5 mg Cd/kg/day) for 500 days. It has been hypothesized that this is not a direct action of cadmium on bone, but is secondary to abnormal metabolism of calcium, phosphate or vitamin D.

Rats which received 50 mg Cd/L in water (about 3.8 mg Cd/kg/day) for 120 days displayed fatty bone marrow and anemia. Similarly, cells of the immune system were adversely affected in rabbits and mice which received from 3 to 300 mg Cd/L in drinking water (about 0.63 to 63 mg Cd/kg/day) for 70 days.

Rats which received 0.1 to 1 mg Cd/kg/day (orally) for 45 days had hyperglycemia and glucosuria. Pancreatic beta cells isolated from these animals showed decreased insulin secretion, but it appeared that increased hepatic gluconeogenesis also contributed to the hyperglycemia.

The role of cadmium in experimental and human "essential" hypertension remains a matter of controversy and conjecture. Rats which received drinking water containing 5 mg Cd/L (approximately 0.5 mg Cd/kg/day) usually developed mild hypertension (systolic blood pressure about 10 to 20 mm Hg above control animals) within several months. However, this effect was not consistently observed. One explanation for the discrepancy may lie in different sensitivities between animal strains and sexes, but variation in diet appears to be a more important factor. Rats fed a special low-cadmium diet (0.02 µg Cd/g chow) have lower blood pressure than rats fed a "standard diet" (containing 0.62 µg Cd/g chow). Moreover, the blood pressure of rats on a "standard" diet tends to increase slowly with age, while the blood pressure of rats on a low-cadmium diet tends to remain constant. Thus, statistically significant blood pressure effects due to very low levels of cadmium exposure (i.e., 0.1 mg Cd/L in drinking water) may be observed in rats on special low cadmium diets, but a higher cadmium exposure (i.e., 5 mg Cd/L in drinking water) is required to produce statistically significant blood pressure changes in rats on a "standard" diet. The genetic background of the individual also plays an important role in determining the sensitivity to cadmium-induced hypertension and its complications.

Several studies in rats have been performed to determine the carcinogenic potential of orally ingested cadmium (at 0.3 to 2.3 mg Cd/kg/day for 1.5 to 2 years). All studies observed no significant ($P>0.05$) increase in tumor incidence in the cadmium-treated animals. Chronic inhalation of cadmium aerosols, however, does result in increases (15% to 71%) in the frequency of lung tumors in male rats.

Cadmium exposure was observed to cause chromosomal aberrations in several in vitro studies, but strong evidence of mutagenic effects following orally ingested cadmium is not available. Cadmium feeding (500 to 1,270 µg/g in food) caused testicular damage in male rats, although 100 mg Cd/L in drinking water did not. Female rats receiving 17 to 100 mg Cd/L in water before or during gestation produce smaller litters and pups of reduced weight. Such effects may be partly due to direct embryotoxic actions of cadmium, but may also arise indirectly from reduced maternal food consumption and metabolism.

Acute human cadmium poisoning is usually the result of ingestion of food or liquids which have been stored in cadmium-plated vessels. The NOAEL for a single oral ingestion in humans has been estimated to be 3 mg (0.043 mg/kg for a 70-kg adult). Higher doses (3 to 300 mg) cause nausea, vomiting, diarrhea, muscle cramps, salivation, liver injury, convulsions, renal failure, cardiopulmonary depression and shock. Doses in excess of 300 mg can be fatal.

In humans, chronic low-level cadmium ingestion in non-occupational settings can result in adverse health effects such as Itai-Itai disease in

Japan. Prominent symptoms of Itai-Itai include osteomalacia, osteoporosis, proteinuria, glucosuria and anemia. The renal injury leading to proteinuria is associated with an increased cadmium content in the renal cortex.

Little information is available regarding the mutagenicity of cadmium in humans. Chromosomal abnormalities have been observed in leukocytes from patients with Itai-Itai, but the lymphocytes appear normal. No evidence has been reported indicating that oral ingestion of cadmium is carcinogenic in humans. Several studies of workers exposed to cadmium via inhalation provided evidence of increased rates of lung, renal and prostatic cancer. However, the data are not sufficient to permit strong conclusions at present, especially with regard to cadmium in drinking water.

Very little is known regarding the biochemical mechanisms by which cadmium causes toxicity at the cellular level. Most researchers hypothesize that cadmium is toxic because it interacts with enzymes (especially metalloenzymes) destroying their activity, or because it interacts with DNA and chromatin. Little data to substantiate these concepts are currently available.

Sensitivity to cadmium is increased by diets deficient in zinc, calcium or protein. Cadmium toxicity is diminished by providing supplemental zinc to the diet. Some chelators administered concurrently with cadmium also diminish its toxicity.

Based on selected animal and human data, a quantitative risk assessment has been performed. Assuming a NOAEL of 0.043 mg Cd/kg following a single oral dose of 3 mg Cd in humans, one-day Health Advisories for children and adults have been calculated to be 0.043 mg/L and 0.15 mg/L, respectively. Using a NOAEL of 0.84 mg/kg/day for subchronic (24 week) oral exposure in rats, the calculated ten-day Health Advisories for children and adults are 0.008 mg/L and 0.029 mg/L, respectively.

An Acceptable Daily Intake (ADI) of cadmium in adult humans was calculated based on the estimate that the critical concentration for renal dysfunction (proteinuria) is 200 µg Cd/g wet weight of renal cortex in humans. This value is based on an extensive review of data from animal studies and analysis of kidney tissue in humans. While individual estimates of the critical renal concentration vary from 50 µg/g to more than 300 µg/g, the best estimate of the critical level is 180 to 220 µg/g. At this level, about 10% of a chronically exposed human population may be expected to display signs of renal dysfunction. The daily cadmium intake resulting in accumulation of 200 µg/g wet weight renal cortex (critical concentration for renal dysfunction) in a human by age 50 is estimated to be 0.352 mg Cd/day. This is based on a model assuming that 4.5% of the daily oral dose is absorbed and 0.01% of the total body burden is excreted daily. Based on this estimated daily cadmium intake (0.352 mg Cd/day) and an uncertainty factor of 10, an ADI of 0.035 mg Cd/day was calculated. Assuming that 100% of the cadmium derives from drinking water, the Adjusted Acceptable Daily Intake (AADI) is 0.018 mg Cd/L.

An AADI based on human data emphasizing renal effects (proteinuria) currently appears to be most appropriate. However, consideration was also given to an AADI based on the NOAEL of 0.003 mg Cd/kg/day from a study of cardiovascular effects (primarily hypertension) in rats exposed to 0.03 mg Cd/L for 15 months. Based on this NOAEL and an uncertainty factor of 100, an ADI of 0.002 mg Cd/day was calculated. Assuming that 100% of the cadmium derives from drinking water, the AADI is 0.001 mg Cd/L (1 μg Cd/L).

The National Interim Primary Drinking Water Regulations maximum contaminant level (MCL) for cadmium is 0.010 mg/L (10 μg/L). The National Academy of Science established SNARLs of 0.150 mg/L (150 μg/L) for single 24-hour exposure, 0.021 mg/L (21 μg/L) for a seven-day exposure and 0.005 mg/L (5 μg/L) for chronic exposure to a 70-kg adult human. The World Health Organization recommended guideline for cadmium in drinking water is 0.005 mg/L. The Commission of European Communities estimated the thresholds for effects from total [illegible]al cadmium intake by adult humans to range from 200 to 248 μg/day for the non-smoker and 169 μg/day for the smoker.

No data exist that suggest orally ingested cadmium is carcinogenic in either animals or humans. Therefore, no estimate of carcinogenic risk due to orally ingested cadmium has been calculated. Cadmium exposure by inhalation may be carcinogenic in animals, but data based on this route of exposure have questionable relevance to exposure via drinking water. The role of cadmium in the induction of cancer remains a matter of controversy and conjecture.

A number of factors such as diet, age, sex, genetic background and cigarette smoking are recognized to influence susceptibility to cadmium toxicity. Animal data suggest that dietary deficiencies of calcium, protein, zinc, iron or copper increase absorption and toxicity of cadmium. No clinical or epidemiological evidence demonstrates that children, as a group, are more sensitive or at greater risk to the adverse health effects of cadmium. However, experimental data indicated that young animals have a greater gastrointestinal absorption and retention in the gut. Females appear to be more sensitive to cadmium toxicity than males. Observations from Itai-Itai disease identified multiparous women (i.e., postmenopausal with several deliveries) to be the group at highest risk. Animal experiments demonstrated that genetic background influences susceptibility to cadmium-induced hypertension and its complications. Cigarette smokers represent a group at increased risk to cadmium exposure and toxicity due to the cadmium content of tobacco and the relatively high cadmium absorption rates via inhalation.

II. GENERAL INFORMATION AND PROPERTIES

A. Chemical and Physical Properties

Discovered in 1817 by Strohmeyer and Herman in Germany, cadmium is a transition metal in group IIb of the periodic table of elements. Cadmium is a soft white metal with a bluish tinge possessing considerable ductility. The atomic weight of cadmium (112.40) is derived from a mixture of eight stable isotopes of natural abundance: ^{106}Cd (1.22%); ^{108}Cd (0.88%); ^{110}Cd (12.39%); ^{111}Cd (12.75%); ^{112}Cd (24.07%); ^{113}Cd (12.26%); ^{114}Cd (28.86%); and ^{116}Cd (7.58%). The chemical and physical properties of cadmium and some of cadmium's principal inorganic salts are listed in Table II-1. Cadmium in compounds has a valence of +2 and the ion is colorless (CEC 1978).

The vapor pressure of cadmium is 1.4 mm at 400°C and 16 mm at 500°C. Losses by vaporization are to be expected during thermal treatment such as ore roasting, brazing, remelting of steel scrap and incineration of cadmium-containing refuse. In air, the vapor oxidizes quickly to produce cadmium oxide. Cadmium dissolves in dilute weak acids, especially nitric acid. The bromide, chloride, fluoride, iodide, nitrate and sulphate salts of cadmium are relatively soluble compounds. Cadmium also forms a wide variety of soluble complexes, notably with cyanides and amines. The carbonate, hydroxide, oxide and sulfide forms of cadmium are insoluble in water (CEC 1978). Cadmium sulfide is decomposed by acids with the liberation of hydrogen sulfide gas.

Table II-1 Chemical and Physical Data

Chemical name	Formula	Chem. abstract reg. serial no.	Atomic/mol. weight	Melting point °C	Boiling point °C	Crystal system	Solubility[a]	Density g/cm^3	Refractive index
Cadmium	Cd	7440-43-9	112.40	320.9	765	hexagonal, silver-white metal	nitric acid (s) sulphuric acid (s)	8.642	1.8 at 578 nm
Cadmium acetate	$Cd(CH_2H_3O_2)_2$	543-90-8	230.50	256	--		water (vs) methanol (s)	2.341	--
Cadmium carbonate	$CdCO_3$	513-78-0	172.41	--	--	trigonal, white powder	acids (s) ammonium salts (s) KCN (s) water (i)	4.258	--
Cadmium chloride	$CdCl_2$	10108-64-2	183.32	568	--	hexagonal, colorless	water (s) methanol (ss) ethanol (ss)	4.047	1.65 at 589.3 nm
Cadmium fluoride	CdF_2	7790-79-6	150.4	--	1,758	cubic, white	water (s) hydrogen fluoride (s)	6.33[a]	1.56 at 589.3 nm
Cadmium molyhdate	$CdMoO_4$	13972-68-4	272.34	--	--	yellow plates	acids (s) NH_4OH (s) KCN (s) water (ss)	5.347	--

continued-

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[a] s = soluble, ss = slightly soluble, bs, = barely soluble, i = insoluble, vs = very soluble.

Table II-1 - continued

Chemical name	Formula	Chem. abstract reg. serial no.	Atomic/mol. weight	Melting point °C	Boiling point °C	Crystal system	Solubility[a]	Density g/cm^3	Refractive index
Cadmium nitrate	$Cd(NO_3)_2$	10325-94-7	236.41	350	--	colorless solid	water (vs)	2.45	--
Cadmium oxide	CdO	1306-19-0	128.40	900 (decomposes)	1,559 (subl.)	cubic, brown	acids (s) ammonium salts (s) water (i) alkalis (i)	8.15	2.49 at 670.8 nm
Cadmium sulphate	$CdSO_4$	10124-36-4	208.46	1,000		rhombic, white	water (s) methanol (bs) ethanol (bs)	4.691	--
Cadmium sulfide	CdS	1306-23-6	144.46	1,750 (100 atm)	980 (subl. in N_2)	hexagonal, yellow-orange	water (i)	4.82	2.529 at 589.3 nm

[a] s = soluble, ss = slightly soluble, bs, = barely soluble, i = insoluble, vs = very soluble.

Adapted from Weast (1971), IARC (1976), Schindler (1967), Parker (1978).

Unlike alkyl mercury derivatives, alkyl cadmium compounds are extremely unstable, reacting rapidly with water and moist air under ambient conditions therefore, alkyl cadmium compounds are not considered important environmental pollutants (CEC 1978). Cadmium is strongly adsorbed to clays, muds, humic and organic materials and some hydrous oxides; cadmium is readily removed from the water column by precipitation (Watson 1973).

B. Manufacture and Uses

Cadmium is ubiquitous in the lithosphere. Cadmium does not naturally occur in the pure state. Cadmium is generally found in association with zinc and lead (CEC 1978). The world production of cadmium, principally from the cindering of flue dusts and roasting of zinc ores, was over 17,000 metric tons in 1976 (Lucas 1977). Production peaked in 1969, but since 1970, the pressure on industry brought about, in part, by concern regarding cadmium in the environment and its effects on human health has resulted in a decline in the worldwide supply of this element. The estimated United States consumption patterns (in metric tons) for cadmium in 1974 were: electroplating, 2718; stabilizers, 906; pigments, 997; batteries, 544; alloys and other uses, 441 (Stubbs 1978).

Electroplating of cadmium on metals such as steel, iron, copper and brass imparts corrosion resistance (Parker 1978). Cadmium plating is used extensively in the automobile, aircraft, machine, marine and electronics industries (Stubbs 1978, Hewitt 1978, Lucas 1977, CEC 1978).

Cadmium is also extensively used in the pigment industry. Cadmium compounds are often the choice pigments, especially in plastics, ceramics, paints, fabrics, textiles, rubber, glass and inks, with no common or readily available substitute. Cadmium pigments are acid sensitive and have generally poor weathering properties. Cadmium is used to stabilize and retard discoloration of polyvinyl chloride (PVC) resin during high temperature molding operations (CEC 1978). The cadmium-barium-(zinc)-epoxy organophosphite stabilizers dominate the flexible PVC market and are used extensively for calendering and plastisols. Cadmium-based stabilizers are not used for food-grade flexible PVC because of potential adverse health effects (Parker 1978).

Nickel-cadmium and some silver-cadmium batteries represent a fast growing segment of the industry consuming cadmium. Sealed nickel-cadmium alkaline batteries are used in radios, alarm systems, emergency lighting, pacemakers, calculators, motor starters, and portable appliances and tools. Vented cell types are much larger and are used in buses, diesel locomotives, aircraft, spacecraft and standby power and lighting (CEC 1978, Parker 1978, Stubbs 1977). Cadmium is also employed in alloys with other metals, compounds with phosphor and luminescent properties, electrical contact materials, photovoltaic solar cells, and photocells (Hewitt 1978). It should be emphasized that most uses of cadmium are completely dissipative and only a small percentage of the consumed cadmium is recycled (CEC 1978). The low rate of secondary recovery has direct consequences on the environmental dispersion and future global resource of cadmium.

C. Summary

Cadmium is an element of transition metal group IIb. It occurs naturally throughout the earth's crust, generally in association with zinc or lead ores. While elemental cadmium is insoluble in water, it dissolves in weak acids, and many cadmium salts (e.g., $CdCl_2$, $Cd(NO_3)_2$, $CdSO_4$) are quite soluble in water.

Cadmium is manufactured primarily by roasting cadmium-containing ores. Cadmium has signficant vapor pressure above 400°C, and cadmium may escape into air during high temperature operations. Cadmium and cadmium compounds have many industrial applications, and are widely used in electroplating, as plastic stabilizers, as pigments, and in batteries. In 1974, over 5,600 metric tons of cadmium were consumed in the United States. Very little recycling of cadmium products occurs at present.

III. TOXICOKINETICS

Data on the absorption, distribution, metabolism, excretion and body burden of cadmium have been derived from experimental studies on animals and humans, studies on populations exposed to varying levels of cadmium and autopsy studies. The data have been obtained by chemical analysis of cadmium, (i.e., spectrophotometry, atomic absorption spectrometry or in vivo neutron activation analysis) or by means of radioactive tracer techniques using cadmium radioisotopes (usually ^{109}Cd or ^{115m}Cd). Much of the present knowledge of cadmium intoxication is based on studies of cadmium metabolism. Nordberg and Kjellstrom (1979) developed a metabolic model for cadmium in the human body on the basis of empirical data from both animals and humans (see section III.B.1.b.).

A. Absorption

1. Gastrointestinal Tract

a. Animal Studies

A relationship exists between the exposure (dose), gastrointestinal absorption and biological half-time of cadmium. Elucidating this relationship is important in characterizing the nonlinear kinetics of the metabolism of cadmium and establishing estimates of exposures which elicit effects.

Engstrom and Nordberg (1979a) administered 1, 15, 750, or 37,500 µg/kg of cadmium as $^{109}CdCl_2$ to groups of ten inbred adult male CBA mice by gavage after two hours of fasting. The ^{109}Cd activity was followed by gamma spectrometric counting of the whole-body for four months and of individual organs after sacrifice. The gastrointestinal absorption of the radiolabeled cadmium (expressed as whole-body retention in percent of administered dose) five days after exposure was 3.2% in the high dose group, 1.4% in two intermediate dose groups and 0.5% in the low dose group. After 140 days, whole-body retention was 2.2%, 0.32%, 0.39% and 0.19% for the highest, two intermediate and lowest dose groups, respectively. The corresponding biological half-time of the retained dose of ^{109}Cd was 70 to 90 days from the low and intermediate dose groups and two- to three-times longer at the highest dose. The dose dependence of the gastrointestinal absorption of cadmium was not previously recognized. The authors suggest that possible mucosal damage occurring at the highest dose may result in enhanced metal absorption, but that increased metallothionein biosynthesis may be responsible for dose dependence seen at intermediate doses.

Nordberg et al. studied the retention of cadmium in monkeys (Saimori sciureus) by whole-body measurements after administration of $^{115}CdCl_2$ by gavage (Friberg et al. 1974). Groups of two monkeys received either 0.17 or 1.7 mg Cd/kg following a 24-hour restriction of solid food; for two hours preceding and four hours following the cadmium-administration, the monkeys had no access to water. Food was also restricted for four hours following administration of cadmium. The monkeys retained 2.5% to 3.2% (average 2.9%) of the ingested amounts of cadmium ten days after ingestion.

Kostial et al. (1983) studied the absorption and retention of cadmium ^{109}Cd in six-day-old suckling and six-week-old weaned rats. The results showed that the sucklings retained a much higher fraction of ^{109}Cd in the carcass, gut and whole-body than the weaned rats. Kostial et al. (1979) also observed that cadmium has a longer retention time in the gut of neonatal rats than in weaned rats.

Decker et al. (1958) administered drinking water containing 0, 0.1, 0.5, 2.5, 5.0 or 10.0 mg Cd/L (approximately 0, 0.008, 0.035, 0.181, 0.361 or 0.735 mg/kg/day, assuming 0.030 L/day and reported body weights of 0.359, 0.433, 0.414, 0.415, 0.408 kg, respectively) as $CdCl_2$ to groups (eight to ten per sex) of 34-day-old albino Sprague-Dawley rats for a 12-month period. One group was administered 50.0 mg Cd/L (approximately 3.04 mg/kg/day, assuming 0.014 L of water/day and a body weight of 0.23 kg) for three months. Total-body retention of cadmium was not measured, but the percentage of the administered dose retained in kidney and liver was determined. Since these organs will accumulate most of the cadmium, this estimate may indicate the whole-body retention (Friberg et al. 1974). Less than 1% of the total ingested amount had been retained in these organs (0.33% to 0.63% at all exposure levels) over the length of exposure. If it is assumed that 50% to 75% of the total body burden is in liver and kidney, total retention would be less than 1% to 2%.

The gastrointestinal absorption studies discussed above are in agreement with most of the literature that indicates that the absorption rate for cadmium is about 2% for most animal species (Friberg et al. 1974) although a range of 0.5% to 12% has been reported (CEC 1978).

Moore et al. (1973) administered a single dose of 50 μCi of cadmium as $^{115}CdCl_2$ by gavage to male COBS rats (number and age not specified). Gamma-ray spectrometry was used to measure whole body radiation every other day for 60 days. Whole-body retention of radiolabeled cadmium declined rapidly within four days to approximately 2.3% of the administered dose. Unabsorbed ^{115}Cd passed rapidly through the gastrointestinal tract accounting for this initial decline in cadmium retention. The subsequent retention followed a first-order exponential curve which reflects the absorption and clearance of cadmium. A biological half-time of 206 days was calculated.

Engstrom and Nordberg (1979b) determined whole-body retention, organ distribution and biological half-time of $^{109}CdCl_2$ (50 mg Cd/L as $CdCl_2$, 10 mCi/L given as a single oral dose of 10 to 20 μg) in CBA mice to examine the effect of age, pretreatment with $CdCl_2$ and long-term treatment with $CdSO_4$. The experiment on groups of eight to ten male mice, 1, 3 and 6 months of age, showed that whole-body retention of radiolabeled cadmium was inversely related to age; the youngest mice had concentrations of ^{109}Cd two to three times higher in all organs examined compared to adult mice, and 4.5 to 8 times higher than older mice. In a second experiment, three groups of eight to ten adult mice were pretreated with 75 mg $CdCl_2$/L in drinking water for 0, 13 or 130 days before receiving the single oral dose of ^{109}Cd. A higher intestinal absorption of radiolabeled cadmium and a longer biological half-time of ^{109}Cd was observed in pretreated mice as compared to controls. Absorption for the three groups, expressed as percent of radiolabeled dose (day after dosing), was 0.40%, 0.87% and 0.96%, respectively. The total biological half-time of ^{109}Cd counted from day seven after exposure was 78, 145 and 292 days, respectively.

In a third experiment, male and female mice (eight mice/sex/group) were given an acute ^{109}Cd oral dose and thereafter given either deionized water or 50 mg $CdSO_4$/L in the drinking water continuously for 18 months. The organ retention of the radiolabeled cadmium was higher in the mice exposed to cadmium in drinking water compared to the mice given deionized water. Mice exposed to cadmium via drinking water had a markedly longer biological half-time of ^{109}Cd than mice not exposed to cadmium. In all experiments the animals retaining a larger proportion of the cadmium dose showed higher liver:kidney ratios of the radiolabeled cadmium than mice retaining less cadmium.

Several reports have demonstrated that dietary factors may exert a profound influence on the gastrointestinal absorption and metabolism of cadmium. Diets low in calcium lead to significantly higher absorption and deposition of cadmium into intestinal mucosa, liver and kidneys and corresponding decreases in fecal excretion in rats (Washko and Cousins, 1976). Milk diets have been reported to increase cadmium absorption (Kello and Kostial 1977); furthermore, the cadmium concentrations in milk from 61 American cities are relatively high (17 to 30 ppb) in comparison to water standards (Flick et al. 1971). Experiments with chickens given a vitamin-D deficient diet with a vitamin D supplement reveal increased cadmium absorption as compared to those on the deficient diet only (Worker and Migicovsky 1961). Low protein diets also result in considerably higher levels of cadmium in various organs irrespective of the calcium content of the diet (Suzuki et al. 1969). Dietary pyridoxine (vitamin B_6) has been reported to influence cadmium absorption in rats (Stowe et al. 1974).

Ascorbic acid supplements have been found to reduce cadmium toxicity (Fox and Fry 1970). Deficiencies of zinc, iron and copper have been claimed to enhance cadmium uptake and subsequent adverse effects (Banis et al. 1969, Bunn and Matrone 1966), but no effect of zinc deficiency on cadmium uptake was observed by Hahn and Evans (1975) or Foulkes and Voner (1981).

It must be emphasized that Cd absorption in the presence of food may differ very greatly from its absorption from water. Thus, milk placed into the rat jejunum reduced Cd uptake from a salt solution by 50% (Foulkes 1980). The composition of food also greatly affects Cd retention (Rabar and Kostial 1981).

Bhattacharyya et al. (1981) studied the influence of pregnancy and lactation on the gastrointestinal absorption and retention of cadmium in B6CF$_1$/Anl mice. A single dose (5 μCi) of $^{109}CdCl_2$ was administered orally to the mice (after 18 hours of fasting) on a given day of gestation (day 8 or 15) or lactation (day 3, 10, 17 or 24). The amount of cadmium in whole mouse (minus gastrointestinal tract) and selected organs was measured 72 hours later. When cadmium was administered during gestation, a slightly greater fraction was absorbed and retained, but the differences were not statistically significant. However, when cadmium was given during lactation, statistically significant increases in absorption and retention of the metal were observed on days 10 and 17 ($P<0.01$). By day 24, there were no differences when compared to nonpregnant controls. Deposition of cadmium in the kidney reflected the changes in gastrointestinal absorption but deposition in the liver was not altered by gestation or lactation. Retention of cadmium by the duodenum was similar to that of the kidney but an increase in metal retention was also observed on day 1 of lactation. Thus, during gestation and lactation the most striking changes in gastrointestinal absorption of cadmium occurred during mid-lactation. Representative results are shown in Table III-1.

In companion studies, Bhattacharyya et al. (1982) also examined the absorption and retention of ^{109}Cd during gestation and lactation in female B6CF$_1$/Anl mice given cadmium in drinking water in low concentrations (0.03 µCi or 0.11 ppb Cd). During gestation, lactation, or a combined period of gestation and lactation, the mice retained two- to three-times more cadmium than did nonpregnant controls. The ^{109}Cd contents of various tissues were also strikingly increased. Increases in kidney (fivefold) and mammary tissue (ninefold) were apparent during lactation. These results suggest that pregnant and lactating mice absorb and retain substantially more cadmium than do nonpregnant mice.

b. Human Studies

McLellan et al. (1978) used a whole-body counter to determine cadmium absorption and excretion in 14 healthy humans (21 to 61 years old, sex not specified) and in one patient with an ileostomy. The participants fasted overnight and then ate breakfast and a drink containing 5 µCi cadmium as ^{115}CdCl$_2$ (0.42 Ci/g) and 2 µCi ^{51}CrCl$_3$ (125 Ci/g). The meal contained a total of 22 to 29 µg cadmium as determined by atomic absorption spectrometry. The participants then fasted for two hours. Four hours after the meal, radioactivity of ^{51}Cr and ^{115}Cd was measured on the whole-body counter.

Table III-1 Cadmium Concentrations in Mouse Tissues 72 hours After Administration of Cadmium on Various Days of Gestation and Lactation

Sample	Cadmium concentration % dose/g ($\times 10^2$)[a]						
	Nonpregnant controls(8)[b]	Gestation day 8(8)	Gestation day 15(5)	Lactation day 3(10)	Lactation day 10(10)	Lactation day 17(8)	Lactation day 24(10)
Liver	10.8±0.7(43.7)[c]	13.5±2.8(42.8)	10.1±3.5(53.9)	3.9±0.4[d](34.3)	6.2±0.7(30.2)	6.9±1.9(32.9)	6.3±0.8(50.0)
Kidney	21±2(19.3)	36±9(26.4)	24±6(22.4)	21±3(28.4)	43±4[d](34.8)	54±10[e](42.9)	17±3(25.6)
Mammary tissue	0.2±0.02(3.1)	0.2±0.05(1.4)	0.2±0.05(2.1)	0.7±0.06[d](13.0)	0.9±0.08[d](11.4)	1.2±0.3[e](12.3)	0.5±0.1(9.6)
Lung	0.2±0.04	0.2±0.1	0.40±0.05	0.2±0.05	0.2±0.08	0.3±0.1	0.3±0.03
Reproductive tract	0.2±0.03	0.2±0.07	0.3±0.08	0.5±0.07[d]	0.3±0.1	0.2±0.1	0.2±0.02
Remaining carcass	0.7±0.2(33.3)	0.8±0.1(29.2)	0.3±0.05(13.9)	0.4±0.07(24.2)	0.8±0.3(23.5)	0.5±0.1(12.6)	0.2±0.03(14.8)
Stomach	8.0±0.5[c]	9.2±3.2	6.2±1.3	5.1±2.4	5.6±1.6	3.5±0.8	4.2±0.9
Duodenum	31±2	42±14	112±24[d]	184±25[e]	202±35[e]	145±29[e]	26±7
Jejunum	23±6	24±8	10±2	12±2	16±2.6	18±7	9±2

continued-

Table III-1 - continued

Sample	Cadmium concentration % dose/g $(x10^2)^a$						
	Nonpregnant controls(8)[b]	Gestation day 8(8)	Gestation day 15(5)	Lactation day 3(10)	Lactation day 10(10)	Lactation day 17(8)	Lactation day 24(10)
Remaining GI tract	18±2	32±11	20±3	20±3	14±2	16±3	10±2

[a] Concentrations of ^{109}Cd in tissues indicated were determined 72 hour after cadmium administration.
[b] Number in parentheses are numbers of mice per group.
[c] Values presented are means ± SE. Numbers in parentheses are percentages of whole-body cadmium (minus gastrointestinal tract) present in the whole organ.
[d] Significantly different from nonpregnant control values, P<0.05.
[e] Significantly different from nonpregnant control values, P<0.01.

Adapted from Bhattacharyya et al. (1981).

Additional whole-body radiation counts were made at least once a week until no more isotope was detected. The radiolabeled chromium was administered to mark the complete elimination of unabsorbed radiolabeled cadmium from the gastrointestinal tract. Radiolabeled chromium was completely eliminated prior to completion of fecal elimination of cadmium, suggesting that cadmium was returned to the intestinal lumen from the mucosa or through biliary or enteric secretion. There was a rapid initial disappearance of ^{115}Cd: an average 86% of the dose was excreted in the first week. Thereafter, cadmium elimination was slow and variable for one to five weeks and paralleled the loss of the chromium marker. An average of 5.9% of the administered cadmium dose was retained in the body at the point when ^{51}Cr was completely eliminated. No correlation was found between the rate of ^{51}Cr loss and body retention of ^{115}Cd. Subsequent measurements of radiocadmium 7 to 14 days later revealed an average decline in body radioactivity of 13%. This decrease is 10 to 50 times greater than that predicted from the biological half-time of radiocadmium in the body and probably represents excretion of radiocadmium from the gastrointestinal tract. Between 7 and 14 days after complete elimination of ^{51}Cr the mean body retention of radiocadmium was 4.6 ± 4.0% (SD) with a range of 0.7% to 15.6%. The patient with the ileostomy eliminated 87% of the cadmium in the first day with the loss continuing until the study was terminated on day 7.

Shaikh and Smith (1980) administered ^{115m}Cd or ^{109}Cd orally to seven male and five female volunteers and performed whole-body counts for up to 808 days. Estimated absorption in these 12 subjects ranged from 1.1% to 7.0%, with a mean value of 2.8%.

Yamagata et al. (1975) cultured rice plants on a nutrient solution containing 1 mCi of ^{115}Cd. The rice was cooked and 20 g containing 1.3 µCi ^{115}Cd was administered orally to a 53-year-old healthy male subject. A whole-body counter was used to determine the distribution of radiolabeled cadmium at intervals for six days. About 93% of the administered dose was excreted within three days; the total body burden after six days was 4.4% of the administered dose. An acid solution of 1 µCi was administered orally to two male subjects (53 and 49 years old) and the radioactivity of their excreta was measured for three days. The two subjects excreted 71% and 76% of the administered dose, respectively. These excretion values were significantly smaller than those in the case of administration of metabolized ^{115}Cd (rice), suggesting that different chemical and/or physical forms of cadmium may affect absorption. This also raises the potential importance of the effect of different transit times in the gut. The biological half-life of 20 or more years for cadmium was predicted on the basis of an exponential model and these data.

2. Skin

Cadmium is not readily absorbed by skin (CEC 1978). Skog and Wahlberg (1964) applied solutions of 0.005, 0.080, 0.239, 0.398, 0.753 or 4.870 M of $^{115}CdCl_2$ to male and female guinea pigs (10/group). Using an isotope technique (disappearance measurements), 1.8% of the metal was found to be absorbed from the 0.239 M solution over a five-hour period; at lower concentrations less than 1% was absorbed.

3. Respiratory Tract

a. Animal Studies

Studies on animal inhalation of cadmium are limited in number. Some of the data are not useful for detailed calculations of percentage of cadmium absorption. The contribution of cadmium from direct absorption by the lungs and secondary absorption via the gastrointestinal tract following mucociliary clearance has not been determined. Moore et al. (1973) exposed (head only) male COBS rats (number and age not specified) to an atmosphere containing 1800 µg Cd/m^3 (absolute mean diameter of 0.5 µm; $^{115m}CdCl_2$ and $CdCl_2$ mixture with 104.2 µCi/mg) for four hours and monitored them with whole-body gamma spectrometer counting for 60 days. The whole-body retention curve showed an initial decline during the first four days reflecting mucociliary clearance of cadmium from the lungs and passage of the nonabsorbed cadmium through the digestive tract. A second, slower component of the retention curve represented the summation of primary absorption (or deposition) by the lungs and secondary absorption by the gastrointestinal tract. The average retention of cadmium in the lungs immediately following exposure was about 11%. Extrapolation of the second component to the intercept gave an initial absorption value of 41%.

b. Human Studies

Inhalation of cadmium is not an important route of exposure for the general population relative to ingestion. The amount of cadmium deposited in the lower respiratory tract has been estimated to range from 0.0005 to 3.5 µg/day (CEC 1978). Inhalation exposure to cadmium is strongly dependent upon the geographic location and smoking habits of the individual. No precise human data exist that evaluate the bioavailability and absorption of cadmium deposited in the respiratory tract.

Lewis et al. (1972) compared the mean accumulation of cadmium in the kidney, liver and lung of 23 male and 11 female nonsmokers (6.8 mg) and in 138 males who had smoked the equivalent of one pack of cigarettes per day for 40 years (14 mg). A doubling of the cadmium content of liver, kidney and lung of smokers compared to non-smokers was observed. Based on these figures and using typical values for relative distribution of the body burden, cadmium concentration in cigarettes and alveolar deposition, it has been estimated that 64% to 96% of the cadmium deposited is absorbed (CEC 1978). Similar findings (47% to 95%) were reported by Ellis et al. (1979) using *in vivo* measurements of the kidney and liver in smokers and nonsmokers.

Kuhnert et al. (1982) quantified the exposure of pregnant women and fetuses to cadmium as a result of cigarette smoking, and further, evaluated the disposition of cadmium in the maternal-fetoplacental unit. Groups of 41 pregnant smokers and 31 pregnant nonsmokers with similar clinical characteristics were studied. All resided near Cleveland, Ohio. Blood samples were obtained from the mothers during active labor and from the umbilical cord immediately after delivery. A sample of placenta was obtained after perfusion to remove blood. Pregnant smokers expose themselves and their placentas to higher concentrations of cadmium than do pregnant nonsmokers. The mean concentrations of cadmium in maternal blood, cord blood and placental tissues of pregnant smokers were all higher than the mean concentrations of cadmium in the respective tissues of pregnant nonsmokers. The increased tissue concentrations of cadmium in maternal blood (59%) and placental tissue (32%) of smokers was significant ($P<0.01$). While the elevated tissue concentrations were not associated with any adverse effects, the authors concluded that any increase in quantity of absorbed cadmium must be viewed as undesirable.

Buchet et al. (1978) found a higher concentration of cadmium (0.20 versus 0.12 µg/100 mL) in blood of smoking versus nonsmoking European mothers. However, there was no increase in cadmium in the blood of the newborns.

B. Distribution

1. Blood and Internal Organs

Cadmium can be found in blood, internal organs and excreta following exposure via ingestion, inhalation or injection.

a. Animal Studies

Decker et al. (1957) administered 2 mg of cadmium (as the nitrate) containing 10 µCi ^{115}Cd by gavage to male Sprague-Dawley rats (number and age not specified). Eight hours after cadmium administration 54% of the dose was found in the stomach and 44% in the gut; 16 hours later the content decreased to 25% and 34%, respectively; and thereafter to essentially nondetectable levels. Cadmium content of the liver initially rose to 0.75% of the dose after eight hours and then increased to and remained at 1% for 15 days. Fecal content was reported to total 40%, 88%, 93% and 96% of the acute dose after 1, 3, 7 and 15 days, respectively. Little or no radioactivity could be detected in muscle, lung, bone, spleen or urine.

Miller et al. (1968) administered 110 µCi of cadmium (as $^{109}CdCl_2$) in gelatin capsules to three male goats (2.5 months old). Two weeks after the oral dosing, organs and tissue showed a wide variation of ^{109}Cd distribution with averages (as percent of dose/kg fresh tissue) of: 0.122 in hair; 0.022 in skin; 0.021 in testicle; 0.067 in tibia joint; 0.037 in tibia shaft; 1.127 in kidney; 0.029 in muscle; 0.630 in liver; 0.020 in heart; 0.052 in spleen; and 1.040 in duodenum. Much higher levels of ^{109}Cd were found in the liver, heart and spleen of animals given the same dose intravenously. In a follow-up study, Miller et al. (1969) fed six male goats (four- to six-months-old) a control diet or a diet supplemented with 100 mg/L cadmium (as $CdCl_2$) for seven days before administering a single oral dose of 500 µCi of cadmium (as $^{109}CdCl_2$) in a gelatin capsule. After two weeks no significant difference ($P<0.10$) in ^{109}Cd distribution between the two groups was measured; ^{109}Cd distribution in the cadmium-fed group (as percent of dose/kg fresh tissue) was: 1.688 in kidney; 0.5943 in liver; 0.0066 in heart; 0.014 in lung; 0.0055 in testicle; 0.0213 in adrenal; 0.0381 in spleen; 0.0590 in pancreas; 0.0012 in muscle; 0.0063 in skin; 0.0033 in hair; 0.0563 in mesenteric lymph nodes; and 0.0139 in parotid salivary gland. The stable cadmium content in liver, kidney and duodenum after feeding the control or cadmium diet for 21 days was 1.6, 2.7, 2.5 and 17.8, 61.6, 27.5 mg/kg (on a dry matter basis), respectively.

Prigge (1978) fed groups of 12 female SPF Wistar rats (age not specified, 0.170 to 0.190 kg) 0, 25, 50 or 100 mg Cd/L (approximately 0, 2.98, 6.17, or 12.4 mg/kg/day, assuming 0.028 L/day and reported body weights of 0.240, 0.231, 0.223, 0.221 kg respectively) (as $CdCl_2$) in drinking water for 90 days. Dose-dependent increases in cadmium concentrations in whole blood, kidney and liver were found as indicated in the data summarized in Table III-2. As the cadmium dose increased, kidney:liver concentration ratios decreased from 2 to 1.3. In parallel inhalation experiments using similar cadmium oxide concentrations (0, 25, 50, or 100 μg Cd/m^3), liver and blood concentrations were markedly lower than those found in orally exposed rats while kidney cadmium concentrations were comparable.

Bernard et al. (1980) fed two-month-old female Sprague-Dawley rats 0, 2 or 20 mg Cd/L (approximately 0, 0.190, or 1.90 mg/kg/day, assuming 0.028 L/day and a body weight of 0.29 kg) (as $CdCl_2$) for 11 months and 200 mg Cd/L (19.0 mg/kg/day) for eight months via drinking water. There were 40 to 50 rats per dose group. The rate of cadmium accumulation in the liver was lower than in the kidney cortex at low exposures, whereas at the highest exposure the accumulation rates were identical. The cadmium concentration in blood increased to a plateau value after approximately three months of exposure to 2, 20 and 200 mg Cd/L. The plateau value was proportional to the cadmium concentration in drinking water. For all exposure groups, the cadmium concentration in

Table III-2 Cadmium Concentration in Blood, Liver and Kidney of Rats Dosed in Drinking Water for 90 Days

Cd in drinking water (mg/L)	Blood (µg/100 mL)	Liver (µg/g wet weight)	Kidney (µg/g wet weight)
0	-	-	-
25	2.64	6.59	13.11
50	6.36	13.80	27.22
100	14.71	27.34	36.38

Adapted from Prigge (1978).

urine varied more than that in blood. Prior to renal dysfunction, the amount of cadmium excreted in urine tended to increase with duration of exposure. The authors suggest that, at equilibrium, blood cadmium concentrations mainly reflect current exposure; the significant correlation found between the cadmium concentration in the renal cortex and that in the urine confirms earlier hypotheses that the latter is mainly a reflection of the body burden. The data values at the end of the treatment period are summarized in Table III-3.

Sabbioni et al. (1978) conducted a long-term low-level exposure experiment on five-week-old male albino Charles River COBS rats (20 controls, 100 treated animals) to investigate the metabolic patterns for realistic environmental dietary cadmium content. The experiment lasted two years and involved the administration of 61 ppb of cadmium: 50 ppb labeled with ^{109}Cd as cadmium chloride (>15 µCi/µg Cd) via drinking water and 11 ppb unlabeled via food contamination. The total quantity of cadmium ingested over two years was 1550 µg Cd/rat. The average daily intake was 2.1 µg Cd/rat/day. The value corresponds to a daily intake of 4.2 µg Cd/kg for an adult animal. Neutron activation analysis of rat kidneys, liver, testes, spleen, lungs and heart at the beginning of the experiment showed a cadmium concentration ranging from 20 to 35 ng Cd/g of tissue. After two years of exposure, the kidneys were found to contain the greatest concentration with more than 50 ng Cd/g tissue. The small intestine, liver and pancreas concentrations ranged from 3.5 to 5 ng Cd/g tissue. In terms of the total quantity of cadmium per organ, the kidneys retained about 3.5-times as much as the intestine or liver and 40 times as much as the pancreas. Concentrations of 0.1 to 1 ng Cd/g

Table III-3 Cadmium Concentrations in Blood, Liver, and Kidney Cortex of Rats Dosed in Drinking Water for 11 Months

Cd Concentration (mg/L)	Blood (μg/100 mL)	Liver (μg/g wet weight)	Kidney cortex (μg/g wet weight)
0	0.1	0.3	0.5
2	0.5	3	8
20	3.5	20	70
200[a]	18	260	250

[a] Exposed for 8 months.

Adapted from Bernard et al. (1980).

tissue were present in the spleen, lung, testes, heart and brain. The concentration of cadmium in the femur, muscle and fat was less than 0.03 ng Cd/g. Ingestion of 1,550 μg Cd/rat over two years increased the cadmium concentrations of the kidneys and liver by 3.2 and 0.2 times the initial tissue concentration as calculated from ^{109}Cd measurement. The concentrations in spleen, testes, lung and brain increased by factors of 0.01 to 0.03 relative to cadmium concentrations in tissues of young rats at the beginning of the experiment. No significant ^{109}Cd radioactivity was detected in blood at any time during the experiment. The cadmium concentration in most tissues rapidly increased during the first 100 days of exposure. An apparent equilibrium was attained for both the intestine and the liver, while a slight accumulation continued in the kidneys until the end of the experiment. Curves indicative of metal accumulation were observed for ^{109}Cd radioactivity in pancreas, testicles, spleen and lung. The distribution data from the experiment are summarized in Table III-4. The subcellular distributions of ^{109}Cd in whole kidneys, liver, intestine and pancreas were measured at various times of the study (29, 119, 357, 499 and 745 days). These distributions were similar in all organs and were not observed to change appreciably with age. The cytosol soluble fraction contained more than 80% of the total tissue cadmium. Significant amounts of cadmium were also found in other subcellular fractions: the mitochondrial fraction contained 6% to 10%; the nuclear fraction contained 4% to 7%; lysosomes contained 3% to 4%; and microsomes 2% to 4% of the cellular cadmium. Cadmium was dialyzed from the crude cellular organelles from different organs obtained at 119 and 357 days. Forty percent to 60% of the nuclear cadmium was dialyzable while less than 10% could be removed from the other cellular organelles. This suggests that the major portion of

Table III-4 Cadmium Content of Tissue (ng Cd/g wet weight)

Tissue	At the beginning experiment[a]	Uptake of Cd administered during long-term low-level exposure experiment[b]					
		49 days	119 days	217 days	357 days	499 days	745 days
Kidney	19	8.4.±.1.2	20.5±1.2	32.2±2.3	34.5±3.7	45.6±4.7	60.1±6.2
Liver	20	4.1±0.6	3.8±0.6	4.8±0.9	4.5±0.9	4.3±0.6	4.45±0.5
Intestine	--	5.7±1.7	8.1±0.9	8.4±3.2	7.7±1.0	7.9±0.7	8.2±0.7
Pancreas	--	--	2.35±0.04	2.6±0.7	2.8±0.4	3.5±0.7	3.9±0.7
Testicles	27	0.07±0.02	0.12±0.03	0.18±0.03	0.21±0.04	0.31±0.05	0.42±0.1
Lung	35	0.18±0.03	0.26±0.04	0.29±0.07	0.34±0.07	0.52±0.09	0.62±0.07
Spleen	34	0.29±0.15	0.36±0.09	0.52±0.12	0.55±0.1	0.84±0.11	0.96±0.23
Heart	--	0.09±0.023	0.07±0.02	0.13±0.02	0.15±0.04	0.24±0.055	0.29±0.075
Brain	8.7	0.005±0.002	0.012±0.013	0.022±0.005	0.03±0.009	0.056±0.014	0.1±0.03
Muscle	--	0.01±0.003	0.02±0.003	0.02±0.004	0.03±0.008	--	0.04±0.008
Fat	--	--	--	--	0.03±0.02	--	0.03±0.03
Femur	--	0.06±0.014	0.08±0.03	0.08±0.02	0.17±0.04	--	0.15±0.06
Blood	--	<0.001	<0.001	<0.001	<0.002	<0.002	<0.002

[a] Determined by neutron activation analysis.
[b] Determined by ^{109}Cd measurement.

Adapted from Sabbioni et al. (1978).

cadmium in crude nuclei moving from the nuclear fraction to cytosol soluble fraction after washings is a contaminant of cytoplasmatic cadmium binding protein.

Decker et al. (1958) administered 0 to 50 mg/L (0 to 3.04 mg/kg/day) cadmium (as $CdCl_2$) via drinking water to 34-day-old albino Sprague-Dawley rats (8 to 10/dose/sex) for 3 to 12 months. The data for the kidney and liver (as mean ± SD) after one year exposure are summarized in Table III-5. The cadmium content of the kidney and liver increased in direct proportion to the cadmium intake. Tissue concentrations obtained at the end of a year were roughly double those obtained at the end of six months. Kidneys retained two to three times the amount of cadmium found in liver when calculated as μg/g fresh tissue.

Thomas et al. (1980) administered ^{109}Cd once to ten female RF strain mice (age not specified) (0.2 μCi by gavage) and every 28.5 days to a male *Macaca mulatta* monkey (age not specified) (50 μCi on a sugar cube) and a female beagle (50 μCi in chow) and monitored them over a 400-day period. The tissue burdens of cadmium in the monkey and dog are listed in Table III-6. Whole-body biological retention half-lives were determined to be 250 and 531 days for the mice and monkey, respectively.

b. Human Studies

Sumino et al. (1975) examined cadmium concentrations in tissues from 15 male and 15 female Japanese cadavers. The average age of the subjects was 39

Table III-5 Cadmium Content in Liver and Kidney After One Year Exposure

Cd in drinking water (mg/L)	Average Cd intake (µg/rat/day)	Total ingestion (mg/rat/yr)	Kidney		Liver	
			µg/g wet wt	% Cd retained[b]	µg/g wet wt	% Cd retained[b]
0	0	0	0	--	0	--
0.1	3.1	1.132	1.68±0.38	0.30	0.23±0.07	0.21
0.5	15.9	5.750	5.83±2.28	0.20	1.09±0.65	0.16
2.5	82.9	29.820	25.85±9.39	0.16	6.11±2.98	0.17
5.0	150.2	54.360	52.46±3.90	0.17	16.28±4.69	0.26
10.0	276.2	100.00	83.56±24.86	0.17	39.08±12.49	0.35
50.0	700.00	58.8[a]	53.20±8.30[a]	0.16[a]	38.74±9.09[a]	0.47[a]

[a] Values obtained at end of three months.
[b] Percent of total administered dose.

Adapted from Decker et al. (1958).

Table III-6 Tissue Burden of Cadmium in the Monkey and Dog

	% Body burden			
	Monkey[a]		Dog[b]	
Tissue	% Per tissue	% Per g	% Per tissue	% Per g
GI tract	6.60	0.0099	1.03	0.0010
Carcass (remainder)	14.69	0.0019	1.28	0.0014
Brain	0.27	0.0030	0.88	0.011
Heart	0.27	0.0057	1.53	0.012
Lung	0.42	0.0053	0.56	0.0014
Whole blood	0.14	0.0012	0.25	0.00049
Liver	37.49	0.31	38.82	0.0975
Spleen	0.31	0.034	0.45	0.0079
Kidney	38.40	1.24	38.43	0.51
Ovaries	-	-	0.51	0.085
Testes	0.66	0.013	-	-
Muscle	0.46	0.0013	9.20	0.017
Bone	0.28	0.0015	7.07	0.062

[a] Sacrificed 409 to 410 days.
[b] Sacrificed 534 to 535 days.

Adapted from Thomas et al. (1980).

years (range 10 to 60 years) and the causes of death were principally accidental. The data from the study, expressed as μg Cd/g wet weight, are summarized in Table III-7. The greatest concentration of cadmium was found in the kidney. There were significant ($P<0.01$) differences in cadmium concentrations between each of the following tissues: kidney > liver > pancreas > adrenal glands > small intestine. The cadmium concentrations in tissues of females in all age groups were substantially higher than in males, especially in liver and kidney. A total body burden of more than 35 mg Cd was calculated by summing the product of tissue concentrations and tissue weights. The kidney contained 11.7 mg and the liver contained 8.5 mg. Thus, these two accounted for approximately 60% of the total body burden. Cadmium accumulation was higher in females, even when differences in tissue weights were taken into account.

Curry and Knott (1970) performed atomic absorption analysis of liver and kidney samples of autopsy material from 12 men and 8 women (ages 18 to 82 years) in England not knowingly exposed to cadmium. They determined an average kidney concentration of 11.7 mg/kg (range: 2.5 to 19.4 mg/kg) and an average liver concentration of 2.03 mg/kg (range: 1.19 to 3.71 mg/kg). Three long-term industrial intake cases were also analyzed and kidney and liver concentrations determined to be 300, 170, and 70 mg/kg and 200, 180, and 5 mg/kg, respectively. In contrast to many studies demonstrating a steady accumulation of cadmium in human kidney with age, these investigators found no correlation between kidney or liver concentration and age.

Pickston (1981) examined 65 livers obtained from autopsies of accidental death victims and reported a mean cadmium concentration of 1.5 mg/kg, with a

Table III-7 Cadmium Levels in Tissues of Human Cadavers (μg Cd/g wet weight)

Organ	Sex	N	Average	Range	Mean ± SD
Cerebrum	M	10	0.084	0.020 - 0.23	0.12 ± 0.063
	F	11	0.15		
Cerebellum	M	9	0.11	0.030 - 0.23	0.12 ± 0.057
	F	11	0.13		
Trachea	M	12	0.32	0.11 - 0.74	0.36 ± 0.22
	F	4	0.47		
Lung	M	15	0.58	0.15 - 2.3	0.72 ± 0.52
	F	15	0.86		
Heart	M	14	0.16	0.060 - 0.33	0.16 ± 0.69
	F	13	0.17		
Liver	M	15	3.2	1.1 - 23.0	5.7 ± 4.6
	F	15	8.1		
Pancreas	M	15	2.2	0.74 - 8.0	2.7 ± 1.7
	F	15	3.2		
Spleen	M	10	0.40	0.20 - 2.4	0.81 ± 0.69
	F	12	1.1		
Kidney	M	15	36	10 - 94	47 ± 24
	F	15	58		
Adrenal glands	M	13	0.97	0.40 - 4.1	1.5 ± 1.0
	F	13	2.0		
Small intestine	M	13	0.88	0.39 - 1.9	1.1 ± 0.44
	F	14	1.2		
Large intestine	M	14	0.38	0.13 - 0.98	0.43 ± 0.22
	F	13	0.49		
Testicles	M	12	0.52	0.14 - 0.90	0.52 ± 0.24
Ovary	F	12	0.75	0.21 - 1.9	0.75 ± 0.51

continued-

Table III-7 - continued

Organ	Sex	N	Average	Range	Mean ± SD
Muscle	M	11	0.23	0.075 - 1.1	0.29 ± 0.24
	F	14	0.34		
Skin	M	14	0.30	0.045 - 0.94	0.32 ± 0.28
	F	12	0.35		
Blood	M	13	0.16	0.05 - 0.58	0.17 ± 0.11
	F	12	0.21		
Rib (bone)	M	6	0.11	0.04 - 0.21	0.097 ± 0.056
	F	6	0.089		
Fat	F	3	0.068	0.035 - 0.13	-

Adapted from Sumino et al. (1975).

range of 0.2 to 6.2. Kowal et al. (1979) examined residents of Chicago, IL and Dallas, TX, without known high cadmium exposure and reported average concentrations of cadmium of 0.59 to 0.77 μg/L in urine, 0.09 to 0.11 μg/100 mL in blood, and 0.83 to 1.10 μg/g in hair. Autopsy tissues of accident victims in Dallas revealed cadmium concentrations of 21 μg/g in kidney cortex, 1.2 μg/g in liver, 0.067 μg/g in muscle, 0.58 μg/g in pancreas, and 0.040 μg/g in fat.

Miller et al. (1976) reported the results of a survey of cadmium concentrations in whole kidney specimens from 91 Brisbane, Australia post-mortem subjects with ages ranging from 6 months to 93 years. The mean cadmium concentration was 16.8 μg/g, with a range of 1.0 to 40.3 μg/g. When cadmium concentrations were related to the age of the subjects, as demonstrated in several other studies, the metal accumulates in the kidneys until about 50 years of age and then concentrations tend to decrease. Estimates of total body cadmium content from autopsy studies have shown an increase from about 0.1 mg at birth to an adult level of 15 to 30 mg. Friberg et al. (1974) have calculated that about 33% of the total body cadmium is in the kidneys during long-term exposure to small amounts of cadmium. On the basis of this value it is possible to estimate the total body cadmium for a "standard man" of 70 kg; calculations for unexposed populations have resulted in average total body content of cadmium of 15 mg (United Kingdom), 18 mg (Sweden), 10 mg (Germany), 30 mg (USA), 15 mg (Australia), 40 mg (Japan) and 80 mg in the polluted area of Kanazawa, Japan (Friberg et al. 1974, Miller et al. 1976).

Ellis et al. (1981a) measured cadmium in vivo by a neutron activation technique in 83 adult male workers employed in a cadmium production plant and 10 adult males with no known industrial exposure. Since the kidney fits within the dimension of the neutron beam, its total cadmium content can be measured and expressed as mg Cd. The liver is larger then the cross-section of the neutron beam, and so the cadmium content of this tissue is expressed as ppm (μg/g). Cadmium contents of the whole kidney and liver were 0.9 to 57 mg and 0.8 to 120 ppm for the industrial group, compared to 0.4 to 11.8 mg and 0.6 to 7.9 ppm for the control group. At concentrations less than 40 μg/g in the liver, the kidney cadmium burden tended to increase with increasing liver concentration. At concentrations above 40 μg/g, the kidney cadmium content decreased as the liver concentration increased. This change corresponded to a total kidney content of 31 mg. Based on years of exposure and renal dysfunction (β_2-microglobulin, proteinuria) the critical level of 31 to 42 mg cadmium (300-400 μg/g for the renal cortex) was estimated.

Carruthers and Smith (1979) studied 31 residents (14 females and 17 males) of Shipham, England (an old zinc mining area with soil concentrations of cadmium ranging from 60 to 998 μg/g). The home-grown vegetables contained up to 7.34 μg Cd/g dry weight. Drinking water concentrations were not measured. The female subjects (mean age of 48.9 years) had lived in Shipham for an average of 15.1 years. The male subjects were an average of 50.9 years old and residents for 19.4 years. Approximately 53% of the vegetables they ate were home-grown. Blood cadmium concentrations were elevated above normal concentrations (assumed to be <9 nmol/L for nonsmokers and <18 nmol/L for smokers) in nine of the women (range of 15 to 35 nmol/L) and 13 of the men (range of 10 to 133 nmol/L). Some of the subjects had clinical and biochemical evidence of toxicity which the authors attributed to the metal.

Buchet et al. (1980) conducted five annual surveys from 1974 to 1978 on 11- and 12-year-old children in Belgium living 1 km (38 to 56 children) or 2.5 km (29 to 50 children) from a lead smelter and in urban (26 to 29 children) and rural areas (42 to 45 children). Children living less than 1 km from the smelter (air: 0.090 μg Cd/m^3; dust: 197 μg Cd/g) had average blood cadmium concentrations of 0.18 μg/100 mL blood. Children living 2.5 km from the smelter (air: 0.055 μg Cd/m^3; dust: 142 Cd/g) had average cadmium concentrations of 0.11 μg/100 mL) blood. The average blood cadmium values of children living in urban (air: 0.014 μg Cd/m^3; dust: 1 μg Cd/g) and rural (air: 0.012 μg Cd/m^3; dust: 6 μg Cd/g) areas were 0.09 and 0.08 μg/100 mL, respectively. Cadmium content of water was not measured. The authors also reported that, on a group basis, a multiple correlation ($r = 0.96$) between cadmium rinsed from the hand with 0.1 M HNO_3, cadmium concentrations in the air, and cadmium concentrations measured in the blood was evident. Since cadmium in the blood is believed to mainly reflect the amount of cadmium recently absorbed, Buchet and his co-workers, using a multiple regression analysis, estimated that for male children living less than 1 km from the smelter, 30% of the circulating cadmium comes from hand contamination, 30% from inhalation and the remaining 40% from other sources such as food, drink and redistribution from tissues.

Roels et al. (1981a) studied Belgian women over 60 years of age (average age: 81.6 years) living in a cadmium-polluted area (dustfall: 2.5 to >

5 mg Cd/m^2/day) and in two much less polluted areas (dustfall: < 0.0005 to 0.00125 mg Cd/m^2/day). The cadmium concentration in water was not measured. All the women had lived in their respective areas for most of their lives (mean duration: 72 to 75 years). The mean blood cadmium concentration (in µg/100 mL) for women living in the polluted region (N = 60) was 0.16 (range: 0.05 to 0.55) while women living in the two nonpolluted areas (N = 45 and N = 70) was 0.06 (range: 0.01 to 0.28) and 0.12 (range: 0.02 to 0.45).

Hammer et al. (1973) obtained information on age, sex, race, smoking habits and pathologic diagnosis regarding 120 autopsy tissue sets from North and South Carolina. They found that renal cadmium concentrations were higher in males than females, whites than blacks, and cigarette smokers than nonsmokers. Cancer patients had higher and more variable renal cadmium concentrations than noncancer patients. Cadmium concentrations in kidney were found to increase to middle age and then decline somewhat. Mean cadmium concentrations in the renal cortex and liver, expressed as µg/g ash weight, are summarized in Table III-8. The estimated contribution of cigarette smoking to the cadmium body burden in 40- to 70-year-old males was calculated for whole kidney, whole liver and total body burden. For those men who never smoked values were 5.2, 3.7 and 17.8 mg, respectively, while men smoking one-half pack or more daily had values of 11.4, 7.5 and 37.8 mg, respectively. Hammer and co-workers conclude their report by stating that studies characterizing body metal burdens or relating specific metals to disease will be hopelessly confounded unless pertinent covariates such as age, sex, race, cigarette smoking and diagnoses at death are considered.

Table III-8 Mean Cadmium Levels (µg/g ash weight) in the Renal Cortex and Liver of Cadavers

Age interval in years[b]	Renal cortex				Liver[a]	
	Males		Females		Males and females	
	Mean	Range	Mean	Range	Mean	Range
0-9	-	-	-	-	39	8-115
10-19	1,221 (2)[c]	551-1,891	881 (2)	832-929	168	124-247
20-29	1,469 (8)	972-3,164	1,285 (4)	934-1,622	140	21-396
30-39	2,601 (4)	1,797-3,350	1,988 (3)	1,282-2,530	194	21-343
40-49	2,064 (10)	710-3,347	2,062 (6)	1,268-3,200	197	58-375
50-59	2,941 (9)	2,000-4,000	2,197 (4)	1,230-2,850	206	73-368
60-69	1,743 (12)	860-3,450	1,804 (4)	608-3,000	198	21-460
70-79	1,878 (8)	768-4,771	1,509 (4)	455-3,700	273[d]	65-1,720
80-89	940 (1)	-	1,431 (2)	1,350-1,512	282[d]	168-684
90-99	-	-	-	-	97	21-173

[a] No systematic difference by sex noted.
[b] Excludes 15 subjects with cancer, 1 with scleroderma and 1 with hepatitis/pancreatitis.
[c] Number of study subjects in parentheses.
[d] Median.

Adapted from Hammer et al. (1973).

Nordberg and Kjellstrom (1979) have formulated a metabolic model for cadmium in humans in terms of a flow scheme for the metal among eight body compartments. (See Figure III-1). Coefficients for the flow of cadmium were estimated from empirical data both from animals and humans. The presentation of the model here serves to summarize the current understanding of the toxicokinetics of cadmium:

where:

A = amount airborne cadmium inhaled

G = amount of cadmium ingested

C = coefficients as quantity, time, or proportions without units as appropriate

I = daily uptake into systemic circulation

B1 = plasma and plasma protein binding sites

B2 = accumulation of cadmium in erythrocytes

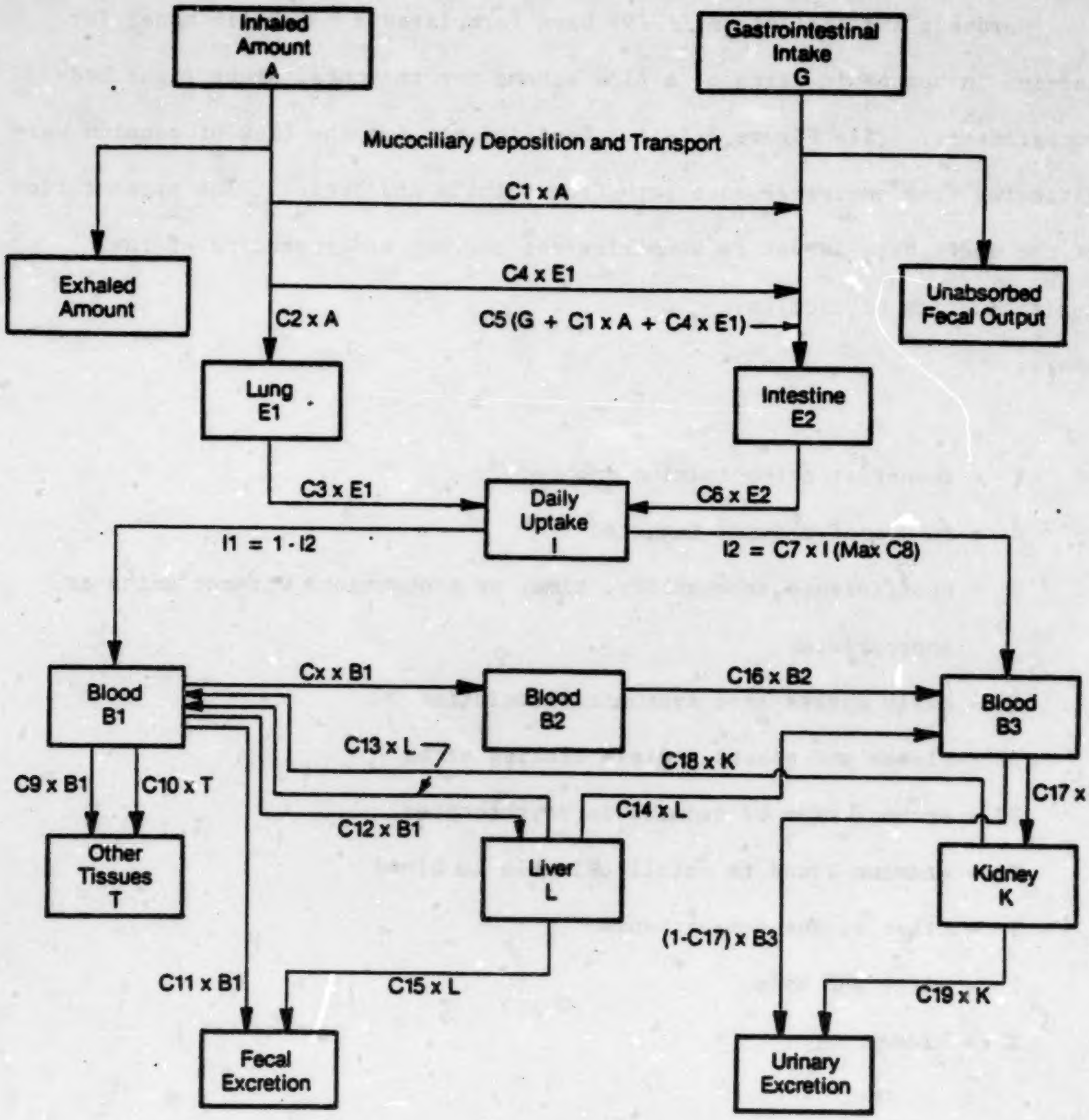
B3 = cadmium bound to metallothionein in blood

T = other tissue compartments

L = liver and bile

K = kidney

The authors did not cite values for the above variables. The flow of cadmium between the compartments in the model is described by a series of differential equations listed in Table III-9.


Inhaled Amount A
Gastrointestinal Intake G
Mucociliary Deposition and Transport
C1 x A
Exhaled Amount
C4 x E1
C2 x A
C5 (G + C1 x A + C4 x E1)
Unabsorbed Fecal Output
Lung E1
Intestine E2
C3 x E1
Daily Uptake I
C6 x E2
I1 = 1 - I2
I2 = C7 x I (Max C8)
Blood B1
Cx x B1
Blood B2
C16 x B2
Blood B3
C13 x L
C18 x K
C9 x B1
C10 x T
C14 x L
C17 x B3
C12 x B1
Other Tissues T
Liver L
Kidney K
(1-C17) x B3
C11 x B1
C15 x L
C19 x K
Fecal Excretion
Urinary Excretion

Adapted from Nordberg and Kjellstrom (1979).

FIGURE III-1 FLOW SCHEME FOR CADMIUM AMONG EIGHT BODY COMPARTMENTS

Table III-9 Values for Variables in Metabolic Model

Compartment	Equation
Lung, exogenous compartment	$E_1(t + 1) = E_1(t) + C_2 \times A(t) - E_1(t) \times (C_3 + C_4)$
Intestines, exogenous compartment	$E_2(t + 1) = E_2(t) + C_5 \times [G(t) + C_1 \times A(t) + C_4 \times E_1(t)] - C_6 \times E_2(t)$
Daily absorbed amount of cadmium	$I(t + 1) = C_3 \times E_1(t) + C_6 \times E_2(t)$ $I_2(t + 1) = C_7 \times I(t + 1) < C_8$ $I_1(t + 1) = I(t + 1) - I_2(t + 1)$
Blood compartment 1	$B_1(t + 1) = I_1(t + 1) + C_{10} \times T(t) + C_{13} \times L(T) + C_{18} \times K(t)$
Blood compartment 2	$B_2(t + 1) = B_2(t) - C_{16} \times B_2(t) + B_1(t) \times (1 - C_9 - C11 - C12)$
Blood compartment 3	$B_3(t + 1) = I_2(t + 1) + C_{14} \times L(t) + C_{16} \times B_2(t)$
Whole blood	$B_4(t + 1) = B_2(t + 1) + C_{20} \times [B_1(t + 1) + B_3(t + 1)]$
Liver	$L(t + 1) = L(t) + C_{12} \times B_1(t) - L(t) \times (C_{13} + C_{14} + C_{15})$
Kidney	$C_{19}(t) = C_{19}$ if $t \leq 30$ years $C_{19}(t) = C_{19} + C_{21} \times n$, if $t > 30$ years $n = 1,2,3.........$; n increased once/year $K(t + 1) = K(t) + C_{17}(t) \times B_3(t) - C_{18} \times K(t) - C_{19}(t) \times K(t)$
Other tissues, endogenous compartment	$T(t + 1) = T(t) + C_9 \times B_1(t) - C_{10} \times T(t)$
Whole Body	$W(t + 1) = B_4(t + 1) + L(t + 1) + K(t + 1) + T(t + 1) = E_1(t + 1) + E_2(t + 1)$
Fecal excretion (excluding nonabsorbed cadmium from GI intake)	$F(t + 1) = C_{11} \times B_1(t) + C_{15} \times L(t)$
Urinary excretion	$U(t + 1) = B_3(t) \times [1 - C_{17}(t)] + K(t) \times C_{19}(t)$

Adapted from Nordberg and Kjellstrom (1979).

2. Placental Transfer

a. Animal Studies

Friberg et al. (1974) suggested that the placenta constitutes an effective barrier against the transfer of low concentrations of cadmium to the developing fetus due to reports of low accumulations of cadmium in fetuses of several experimental animal species. For example, after 12 days of gestation, rat fetuses obtained from dams previously dosed with 0.1 to 0.6 mg Cd/kg accumulated between 0.0001% and 0.0095% of the maternal dose, while placentas accumulated 0.063% to 0.206% (Sonawane et al. 1975). Kelman and Walter (1977, 1978) contend that only a minimal barrier exists against the transfer of cadmium from mother to fetus. Kelman and Walter (1977) perfused the fetal circulation of ten guinea pig hemochorial placentas (61 to 63 days gestation) from six dams (N = 145 perfusion samples) _in situ_ to distinguish fetal uptake from placental transport of cadmium. The clearance of 100 µCi of ^{115}Cd injected via the maternal jugular vein was 0.361 ± 0.003 mL/min at a perfusion rate of 2.5 mL/min. The clearance of cadmium was more than twice the clearance rate of methylmercury (0.15 mL/min) and faster than that of calcium (0.27 mL/min). The cadmium clearance was linearly related to the perfusion rate. Intravenously administered cadmium is rapidly removed from maternal circulation and sequestered in the liver and kidney, so the reported low amount of cadmium transferred to the fetus for many species may reflect low plasma cadmium concentrations in the dam rather than a strong placental barrier. However, the embryolethality of cadmium is not completely explained by the direct effects of the metal on the fetus. Levin and Miller (1978) administered 40 µmol cadmium (as the chloride) subcutaneously to Wistar rats (N = not specified) and found placenta cadmium of 36 ± 0.23 moles and fetal body burdens of 6 ± 0.38 μmoles. To determine whether these amounts of cadmium were lethal to the fetus, the investigators injected the dams or fetuses (2 to 3 μl $CdCl_2$) directly on day 18 of gestation and produced 75% and 14% fetal deaths, respectively. The body burden of the live fetuses injected directly with cadmium ranged from 1- to 20-fold greater than fetal accumulations of cadmium following maternal injections.

b. Human Studies

Chaube et al. (1973) obtained 36 embryos which were from 31 to 78 days of gestational age (first trimester) and 14 second-trimester fetuses ranging in age from 85 to 185 days. The specimens were obtained in Japan following dilation and curettage and were all grossly normal. Embryos in the first trimester of gestation had low whole-body cadmium. Fifty-seven percent (8 of 14) of the samples analyzed contained cadmium concentrations ranging from 0.032 to 0.101 μg/g of wet tissue. Traces of cadmium were found in only 2 of 12 brain samples (0.137 and 0.144 μg/g) and 4 of 14 kidney samples (0.033 to 0.062 μg/g) from the second trimester fetuses. However, cadmium concentrations in 10 of 12 liver samples ranged from 0.036 to 0.22 μg/g of wet tissue. No relationship was found between cadmium concentration and age or sex. Mothers of the abortuses did not reside in areas of Japan where endemic cadmium poisoning exists, though the higher cadmium content of the average Japanese diet may be reflected by cadmium concentrations in these specimens.

Baglan et al. (1974) assayed human samples from hospitals in Nashville, TN, for cadmium content by atomic absorption analysis. Mean elemental concentrations of cadmium, expressed as µg/g dry weight (±SD), were: placenta, 0.102 ± 0.077 (n = 135); maternal blood, 0.093 ± 0.115 (n = 83); and fetal blood, 0.076 ± 0.109 (n = 123). There was a significant (at 95% confidence level) product-movement correlation coefficient of 0.58 between cadmium in placenta and fetal blood but not between maternal blood and placenta or fetal blood. No significant correlations were found with other parameters, such as birth month, gestational age at delivery, race, socioeconomic status and infant status at birth. Cadmium can cross the placenta in humans, but the body burden of the newborn is low since exposure is relatively short (nine months) and a very low concentration is found in maternal blood.

Roels et al. 1978 studied Belgian women and reported that cadmium concentrations in the placenta were about 10 times those in maternal blood, suggesting that the placenta may serve as a partial barrier in the transfer of cadmium from the mother to the fetus. In contrast to the finding of Baglan et al. (1974), Roels et al. (1978) found a weak correlation (r = 0.11) between cadmium in the fetal blood and the placenta.

C. Metabolism

The metabolism of cadmium in animals and humans is greatly influenced by the interaction between the metal and the metal-binding protein metallothionein.

To a significant extent this section will, therefore, focus on this protein. No attempt will be made to exhaustively review the vast literature on metallothionein; reference may be made to two recent review volumes for further detail (Foulkes 1982a, Goyer et al. 1984).

1. Chemistry of Metallothionein

Metallothionein (Mt) is the name given to a family of closely related low-molecular-weight proteins distinguished by their high affinity for heavy metals. Synthesis of these proteins is induced by the heavy metals themselves, as well as by other factors. Although there remains considerable uncertainty as to the precise function of Mt, its biological importance can be inferred from the conservation of its structure throughout evolution (Foulkes 1982a).

The compound was first isolated as a Cd-protein from horse kidney (Margoshes and Vallee 1957). The molecular weight of Mt is around 6,800, and it contains 20 cysteine residues in a total of 61 amino acid residues (Kojima et al. 1976). There are no aromatic amino acids in Mt. The cysteine residues account for the tight binding of metals, especially of cadmium: seven atoms of cadmium are required to saturate the binding capacity of one molecule of Mt (Kagi and Vallee 1961). The amino acid sequence has been fully elucidated (Kojima et al. 1976). Analysis of the ^{113}Cd-NMR spectrum has identified two separate metal clusters in the molecule (Otvos and Armitage 1980); however, their biological role is unknown. Several isomers of Mt have been isolated from various tissues; in addition, the metal composition of the protein affects its properties.

The affinity of cadmium for Mt (association constant of $10^{25.5}$, Kagi and Vallee 1961) exceeded that of zinc (10^{21}). Cadmium in turn is displaced by copper and mercury. This forms the basis of one common method of analysis (Piotrowski et al. 1973) that measures the mercury content of tissue supernatants incubated with $HgCl_2$ and precipitated with trichloroacetic acid. Several variations on this procedure have been proposed, combining metal saturation with gel filtration and taking advantage of the heat stability of Mt. None of these procedures have proved very satisfactory for analysis of the low levels of Mt normally found in blood or urine, but the development of radioimmune assays in several laboratories (e.g., Garvey 1984) has increased the sensitivity and specificity of available techniques.

Metallothionein has been detected in many animal tissues, including placenta, spleen and intestinal mucosa in animals (CEC 1978). Metals other than cadmium can bind metallothionein in vivo, e.g., Zn, Cu, Hg, Ag and Sn (Sabbioni and Marafante 1975). However, no in vivo binding of Ni, Ir, V, Te, As, Mn, Se, Co, Mo or Bi to metallothionein was observed in rat liver (Sabbioni and Marafante 1975). There are multiple forms of metallothionein with different isoelectric points in the rat liver that can interact very strongly with a glycosaminoglycan, forming a number of adducts with different isoelectric points or molecular weights (Webb and Stoddart 1974).

2. Roles of Metallothionein

If Mt functions in the homeostatic regulation of essential metals like zinc and copper, then its induction by, and binding of metals like cadmium and mercury represent extensions of this normal function to other thiol-reactive metals (Webb and Cain 1982). There is no direct proof for this view. It is known, however, that prolonged low-level exposure to cadmium permits accumulation of high body burdens of the metal without ill effects (Yoshikawa 1970). The development of such a tolerance toward the metal may be related to the induction of Mt (Webb and Magos 1976).

A problem with this interpretation is posed by the observation that in relatively high concentrations, exogenous cadmium metallothionein (CdMt) is very nephrotoxic (Cherian et al. 1976). This finding can be explained using an analogy with the toxic properties of other cadmium-thiol compounds (Foulkes 1974), in terms of the ability of renal tubule cells to take up such complexes both following their filtration at the glomerulus and also directly from blood. In the absence of low molecular weight chelating compounds, plasma cadmium is bound primarily to non-filterable and non-diffusible protein. If cadmium, in the form of CdMt, reaches the brush border membrane in the proximal tubule it is readily reabsorbed by a process specific for anionic protein (Foulkes 1978). The process presumably involves endocytosis and lysomal digestion as demonstrated for other proteins (Foulkes 1982b). The freed cadmium is believed to be responsible for the toxic effects of cadmium exposure and also presumably induces the synthesis of endogenous Mt.

Kotsonis and Klaassen (1978) examined the relationship of metallothionein to the toxicity of cadmium after prolonged oral administration to rats. Male Sprague-Dawley rats (initially 50- to 70-days-old) were given 0, 10, 30 or 100 mg Cd/L (as $CdCl_2$) via drinking water for up to 24 weeks. The concentration of metallothionein in the liver and kidney generally increased with dose over the exposure period. The concentration of metallothionein in the kidney was generally greater than that in the liver for all groups except the rats treated with the highest dose. In this group the concentration of metallothionein in the liver and kidney were the same throughout the exposure period. The ratio of cadmium to cadmium-binding capacity of metallothionein in the liver and kidney increased with increasing doses throughout the exposure period (tested at 3, 6, 12 and 24 weeks). Thus, the concentrations of metallothionein and cadmium in the kidney and liver were found to increase with dose at all exposure periods and to increase with exposure period. However, the rates of increase of concentration of metallothionein and cadmium were different in the liver and kidney. In liver, the ratio of cadmium to cadmium-binding capacity of metallothionein reached a plateau after 12 weeks, which the authors suggest may explain hepatic tolerance to cadmium. In the kidney, however, the ratio continued to increase with time, and necrosis and dysfunction were observed (via histopathology and proteinuria).

Endogenous Mt may play a role in the transport of cadmium from liver to kidney. This function was suggested by Piscator (1964) and subsequently discussed by many authors. Quantitative justification for the hypothesis was provided by Johnson and Foulkes (1980). A homeostatic role has been ascribed to Mt at the level of intestinal absroption of metals, especially of zinc (Richards and Cousins 1975). Exposure to metals induces Mt in the intestinal mucosa. Metals taken up from the lumen are trapped by this Mt and subsequently lost to the body upon desquamation of the epithelial cells. A similar role for Mt in cadmium absorption, which has not been fully documented (Kello et al. 1979), would conflict with the claim that CdMt can cross the intestinal mucosa and reach the kidney (Cherian et al. 1978).

Cherian (1979) suggested that experiments with oral administration of the heat-stable cadmium metallothionein complex are relevant to humans since the cadmium in cooked meat, especially kidney and liver, is ingested as the complex. The gastrointestinal absorption and organ distribution of cadmium metallothionein was studied by first isolating the cadmium metallothionein complex from livers of rats injected with $CdCl_2$ and either $^{109}CdCl_2$ or ^{35}S-cysteine. Male mice (four/group) of C57 BL/6J strain (six to ten weeks old) were fasted overnight. One of the following cadmium solutions containing 60 μg cadmium and 2 μCi ^{109}Cd radioactivity was administered by gavage: $^{109}CdCl_2$, ^{109}Cd-cysteine, ^{109}Cd-glutathione, ^{109}metallothionein ($^{109}CdMt$) and ^{35}S-labeled Cd-metallothionein (^{35}S-CdMt). Postmicrosomal supernatant fractions, four hours after oral administration of $^{109}CdMt$ and ^{35}S-CdMt, showed most of the radiolabeled cadmium deposited in the kidney with a major portion bound to high molecular weight proteins, but not metallothionein. There were also small amounts of ^{35}S-labeled cysteine associated with the renal metallothionein, suggesting degradation during the initial period of deposition in the kidney. A major portion of the ingested metallothionein was isolated intact from the intestinal mucosa and considerable amounts of both ^{35}S-labeled cysteine and ^{109}Cd were associated with the metallothionein fraction. Thus, some of the orally administered CdMt reached the small intestine intact and was absorbed without much degradation. A summary of cadmium distribution in tissues four hours after oral administration of the different biocomplexes of cadmium is presented in Table III-10. Except for the CdMt-fed group, a major portion of absorbed cadmium was deposited in the liver. The oral administration of CdMt to mice resulted in an increased deposition of cadmium in the kidney. Similar distributions of cadmium in organs from groups administered the other biocomplexes suggest similar gastrointestinal absorption. The fractionation of the intestinal supernatant showed a similar cadmium binding pattern in all the different groups. The major cadmium binding protein in the intestine was metallothionein. There was, however, an increased amount of cadmium bound to metallothionein in the mucosal cells of CdMt fed mice as compared to groups fed $CdCl_2$, Cd-cysteine and Cd-glutathione.

Shaikh and Hirayama (1979) administered radiolabeled $CdCl_2$ (5 µmol ^{109}Cd/kg) to Wistar rats (sex and age not specified) by subcutaneous injection, five days per week for up to 14 weeks, and measured the radioactive content of whole-body tissues and excreta. The mean renal concentration was 80 µg Cd/g after four weeks. Only 0.01% of the administered cadmium dose was excreted in the urine during the first several weeks. Using gel filtration chromatography, the authors detected metallothionein in plasma after four weeks. The amount of metallothionein in plasma (determined by binding of ^{109}Cd to the 10,000 molecular weight fraction) increased markedly during week 14. Metallothionein was not excreted in urine until about 10 weeks, when the cadmium concentration in the kidney approached a mean of 212 µg/g. From week 10 to 14, glucosuria and proteinuria became severe, indicating renal toxicity. Urinary excretion

Table III-10 Cadmium Distribution in Tissues of Mice Four Hours After Oral Administration of Different Biocomplexes of Cadmium

	Cadmium in organ, ng			
	$CdCl_2$	Cd-Cysteine	Cd-Glutathione	CdMt
Liver	257.7±32	214.3±35	255.8±41	18.1±0.4
Kidney	30.5±3	37.0±6	33.8±3	130.7±0.8
Spleen	6.2±0.9	2.6±.4	2.7±1	2.2±0
Pancreas	9.9±4.3	14.6±4.5	13.1±6	5.5±2
Testes	4.2±0	3.1±0.7	3.2±0.9	2.0±0
Heart	7.1±1.5	5.4±0.9	4.1±0.1	0.9±0.6
Lung	5.5±0.5	5.6±3.2	3.9±0.1	4.3±0.1

Adapted from Cherian (1979).

of cadmium, primarily in the form of metallothionein, increased markedly. The authors suggest that the presence of metallothionein in plasma and urine were indices of cadmium poisoning.

3. Human Studies

Metallothionein has been detected in human kidney, liver, heart, brain, testes, skin epithelial cells and in human embryonic fibroblasts from skin, muscles and lung (CEC 1978). Syversen (1975) examined 40 liver and kidney autopsy specimens from Norway and, using Sephadex chromatography, detected cadmium-metallothionein in 19 of the patients. Syversen divided the patients into three groups: 14 patients who had a small amount of metallothionein (Group 1); five patients with a definite, large quantity of metallothionein (Group 2); and a reference group in which no metallothionein could be detected. Cadmium concentrations (expressed as µg/g tissue dry weight ± SD) and subject variables are summarized in Table III-11. None of the patients had a history of occupational exposure to cadmium. The mean age of the reference group is higher than that of those whose tissues contained metallothionein. The author suggests that the absence of metallothionein combined with a low body burden is associated with longevity. However, it must be noted that the percentage of non-smokers is much higher in this group. Detectable amounts of metallothionein increased with an increasing cadmium body burden.

Chang et al. (1980) used a radioimmunoassay to measure urinary metallothionein in cadmium-exposed and nonexposed workers. Urine and blood

Table III-11 Cadmium Concentrations in Autopsy Specimens (μg/g tissue dry weight ± SD) and Some Subject Parameters

	Reference Group	Group 1	Group 2
Number	21	14	5
Mean age	70	59	60
Range age	50-82	43-91	54-74
Smoking, percent	47	64	80
Died from cardiovascular disease, percent	55	57	80
Liver	6.3±4.9	9.1±4.0	12.2±4.2[a]
Kidney cortex	83±15	152±20[b]	219±51[b]
Kidney medulla	49±19	95±28[b]	147±21[b]

[a] $0.01<P<0.025$.
[b] $P<0.0005$

Adapted from Syversen (1975).

samples were collected from four groups of individuals: Group 1 consisted of eight people from Syracuse, NY who had no occupational exposure to cadmium; Group 2 consisted of eight individuals employed in a primary cadmium smelter plant in Belgium but who did not handle the metal; Group 3 consisted of eight workers in a Belgian factory producing cadmium salts whose average time of exposure was 2.5 years (range: 0.1 to 5.2 years) and who were exposed to high concentrations of cadmium (median 500 μg Cd/m^3 as dust and fumes) (Lauwerys et al. 1979). Group 4 consisted of 16 workers exposed (in the same smelter as Group 2) for an average of 26 years (range: 12.8 to 40.5 years) to moderately high concentrations (median: 50 μg Cd/m^3 as dust and fumes). The majority of workers were smokers and none wore respiratory protective devices. A summary (the mean values and range) of the sample analysis and age of the individuals is presented in Table III-12. No individuals in Groups 1 and 2 had signs of kidney dysfunction. Two workers (25%) in Group 3 and 11 workers (68%) in Group 4 had increased urinary excretion of low and/or high molecular weight proteins, indicating impaired renal function. The exposed workers' urinary concentration of metallothionein is more closely related to urinary cadmium concentration than to renal status. The urinary log cadmium concentration and log metallothionein concentration were significantly correlated ($r = 0.94$; $P<0.05$). The log cadmium concentration in blood and log metallothionein concentration in urine were also significantly correlated ($r = 0.82$; $P<0.05$). These results do not indicate that cadmium-metallothionein is itself nephrotoxic. The urinary metallothionein concentration in normal, nonexposed individuals is typically below the detection limits (100 to 200 pg) of the radioimmunoassay method.

Table III-12 Summary Age and Sample Analysis of Cadmium Exposed and Nonexposed Workers

	Group 1 no exposure	Group 2 low exposure	Group 3 short-term high exposure	Group 4 long-term moderate exposure
Number of Workers	8	8	8	16
Age, years	25.1 (23.4-29.1)	57.1 (48.1-64.3)	32.6 (23.8-46.3)	54.9 (41.8-62.5)
µg Cd/100 mL blood	-	0.36 (0.2-0.5)	13.6 (4.9-18.4)	2.4 (0.7-4.3)
µg Cd in urine/g creatinine	0.2 (0.1-0.34)	2.8 (1.4-5.0)	96.2 (16.6-246.3)	25.1 (9.7-59.3)
µg metallothionein in urine/g creatinine	<0.2	11.8 (2.3-18.6)	551.2 (151.4-1,948.6)	204.0 (16.9-525.9)

Adapted from Chang et al. (1980).

Tohyama et al. (1981b, 1982) collected single urine samples for groups of Japanese women (a total of 67) over the age of 60 years. Urinalyses for cadmium, metallothionein, and β_2-microglobulin were performed. The average urinary metallothionein concentrations of patients with confirmed or suspected cases of Itai-Itai disease were significantly ($P<0.05$) greater than those of women living in a cadmium-polluted area (Jinzu river basin). Excretion of metallothionein was found to be much lower for women residing in a non-polluted area (Kanazawa City) than for women living in the cadmium-polluted area. A similar trend was reported for excretion of urinary β_2-microglobulin, a non-specific index of renal tubular dysfunction. However, mean urinary cadmium concentrations in the Itai-Itai patients, suspected patients and women of the cadmium-polluted area were not significantly different. Specific concentrations for the parameters are listed in Table III-13. Thus, this recent study suggests that urinary metallothionein is a useful index of cadmium exposure.

Tohyama et al. (1981a) conducted a similar investigation in a group of 23 active male workers employed in a cadmium production plant and seven healthy control males. Occupationally exposed workers employed in the factory for periods of 8 to 29 years were found to have significantly higher quantities of cadmium in both liver and kidney (as measured by an in vivo neutron activation technique) and to excrete significantly larger amounts of urinary metallothionein than did workers who were employed for less than one year, office workers at the plant or control subjects without known occupational cadmium

Table III-13 Urinalysis of Cadmium-Exposed Female Subjects[a]

	Group	No. of subjects	Age (years)	Cadmium[b] (μg/g creatinine)	Metallothionein[b] (μg/g creatinine)	β_2-Microglobulin[b] (μg/g creatinine)
I	"Itai-itai"disease patients	18	75.3[c] (60-84)	13.5[c] (9.7-18.8)	1,880[c,d] (1,580-2,230)	91,200[c,d] (75,400-110,000)
II	Suspected patients	21	72.1 (61-84)	16.4[c] (13.4-19.9)	2,000[c,d] (1,630-2,450)	102,000[c,d] (86,200-112,000)
III	Inhabitants of Cd-polluted area	15	74.5 (66-90)	13.8[c] (10.1-18.7)	800[c] (588-1,320)	5,150[c] (1,590-16,700)
IV	Inhabitants of non-polluted area	13	68.7 (60-83)	5.7 (4.3-7.5)	394[e] (292-533)	294 (84-1,030)

[a] Statistical expressions used are: age--arithmetic mean and range; cadmium, metallothionein and β_2--microglobulin-geometric mean and 95% confidence intervals.

[b] Because of the use of spot urine samples, urinary levels of cadmium, metallothionein and $\beta_2$microglobulin were corrected by specific gravity (not shown here) and by creatinine. Statistical treatment of the data corrected by specific gravity gave results similar to those obtained after correction by creatinine excretion.

[c] Significantly different from Group IV ($P<0.05$).

[d] Significantly different from Group III ($P<0.05$).

[e] The metallothionein level of one sample was below the detection limit (146 μg/L); for conservative statistical comparison, the MT level in this sample was assumed to be equivalent to the detection limit.

Adapted from Tohyama et al. (1981b).

exposures. Values for the four groups of subjects are presented in Table III-14. The log of the concentration of metallothionein in urine was significantly correlated with the concentration of cadmium in both liver ($r = 0.75$; $P<0.01$) and kidney ($r = 0.85$; $P<0.01$).

Falck et al. (1983) examined the relationship between urinary metallothionein, chronic exposure to cadmium and renal dysfunction in 53 occupationally exposed males. Controls consisted of 41 males without any known occupational cadmium exposure. Metallothionein excretion was linearly related to protein excretion, β_2-microglobulin excretion, and a cumulative time weighted exposure (dose). Metallothionein was a better predictor of dose than either beta-microglobulin or cadmium excretion. Metallothionein concentrations were significantly higher in subjects with renal dysfunction. The findings suggest that metallothionein is a good biological indicator of chronic cadmium exposure.

D. Excretion

1. Animal Studies

Following a single oral or parenteral dose of cadmium to animals, small amounts of cadmium are eliminated in the urine. Daily urinary excretion of less than 1.0% of the absorbed cadmium has been observed (Shaikh and Lucis 1972). Based on single intravenous dose experiments with dogs, Burch and Walsh (1959) determined that three to seven years were needed to eliminate 50% of the absorbed cadmium via urine. Evidence exists for low levels of daily

Table III-14 Levels of Tissue Cadmium, Urinary Metallothionein and and β_2-Microglobulin in Adult Human Males

Statistical expressions used are: employment periods (arithmetic mean and range); age (arithmetic mean ± S.E.); cadmium, metallothionein and β_2-microglobulin (geometric mean and 95% confidence interval). To adjust for the multiplicity of comparisons and desired overall significance level (P=0.05) was divided by six since there were six possible comparisons for all pairs of four groups.

Group	Subjects	Employment period (years)	Age (years)	Cadmium Liver (µg/g)	 Kidney[a] (mg)	(Metallothionein[b] (µg/g creatinine)	β_2-Microglobulin (µg/g creatinine)
I	Controls (n = 7)	--	40.3±3.2	3.2 (1.2±5.8)	3.1 (1.2-8.4)	148 (102-216)	60 (26-140)
II	Office workers (n = 7)	16.0 (0.7-34.0)	44.0±4.5	8.6[c] (4.6-16.3)	4.6 (1.8-11.6)	130 (89-190)	120 (34-305)
III	Smelter workers (n = 4)	0.15 (0.1-0.3)	26.3±1.9[d]	2.9 (0.7-11.3)	6.0 (2.6-13.5)	100 (72-139)	45 (9-226)
IV	Smelter workers (n = 12)	15.9 (8.0-29.0)	50.3±2.5	39.2[d] (23.9-64.1)	23.6[d] (18.3-30.3)	331[d] (234-468)	148 (42-522)

[a] Cadmium content in the left kidney. For estimated Cd concentrations (µg/g renal cortex) multiply the whole kidney values (mg) by 10.

[b] Number of subjects below the detection limit (125 µg/l) = Group I, 6; Group II, 6; Group III, 2 and Group IV, 2. For conservative statistical comparison, the level of metallothionein below the detection limit was assumed to be equivalent to the detection limit. The values shown are corrected for creatinine excretion.

[c] Significantly different from Group I($P<0.05$).

[d] Significantly different from other groups ($P<0.05$).

Adapted from Tohyama et al. (1981a).

urinary excretion of cadmium during long-term exposure via repeated parenteral administration (0.25 mg Cd/kg/day) (e.g., less than 1.0% of the daily dose was excreted until the onset of renal dysfunction) (Axelsson and Piscator 1966). Subcutaneous administration experiments in mice have shown that excretion of cadmium prior to tubular dysfunction constitutes an average of 0.01% to 0.02% of the total body burden (Nordberg 1972). The urinary excretion of cadmium, when analyzed on a group basis, is significantly correlated with total body burden in controlled animal studies. The urinary excretion of cadmium increases markedly, (as much as 50- to 100-fold) after tubular dysfunction has occurred (Friberg et al. 1974). The duration of the increased urinary cadmium excretion is not known as a function of kidney cadmium burden.

Miller et al. (1968) orally administered 110 µCi of ^{109}Cd as cadmium chloride to three male goats (2.5 months old) via gelatin capsules. On days one, two and three through seven after exposure 0.025%, 0.004%, and 0.002% of the administered dose was excreted via the urine, respectively. The authors acknowledged the possibility of fecal contamination since the amount of ^{109}Cd excreted in the feces was vastly greater (3,000-fold on day two) than that excreted in urine and excretion values were substantially lower in goats receiving intravenous ^{109}Cd (0.002% to 0.025%), compared to the orally dosed group.

Experiments in rats demonstrated that parenterally administered radiolabeled cadmium was partially excreted (4.97% of the acute dose) in the feces four days after administration (Shaikh and Lucis 1972). Burch and Walsh

(1959) calculated a 419- to 659-day half-time if excretion were to occur via feces alone based on a single intravenous administration of cadmium to dogs. Chronic cadmium exposure via repeated subcutaneous injections also results in some cadmium elimination with the feces though the daily excretion is low (less than 5% of the absorbed dose) (Friberg et al. 1974). Nordberg (1972) observed a ratio of 5 to 25 for daily fecal to daily urine excretion of cadmium after subcutaneous administration. Following exposure the fecal excretion among mice decreased, whereas the urinary excretion remained about the same, thus supporting the contention that urinary excretion is more indicative of cadmium body burden than fecal excretion.

Decker et al. (1957) administered 2 mg $Cd(NO_3)_2$ containing 10 µCi ^{115}Cd by gavage to male Sprague-Dawley rats (number and age not specified). Fecal cadmium concentration was reported to equal 40%, 88%, 93% and 96% of the acute dose after 1, 3, 7 and 15 days, respectively. Miller et al. (1968) orally administered $^{109}CdCl_2$ to goats (previously described) and found that the highest rate of fecal excretion occurred two days after dosing for both orally (59.4%) and intravenously (1.7%) treated animals. The first five days following ^{109}Cd administration, orally dosed animals excreted more than 90% of the dose in the feces compared to 5.6% for animals receiving ^{109}Cd by injection. These results emphasize the importance of cautious interpretation of parenteral administration experiments relative to oral administration experiments. The rate of ^{109}Cd excretion on the fifth day following dosing, as a percentage of administered dose, was consistently higher in intravenously dosed animals than in orally dosed animals. This effect is due to the higher amount of ^{109}Cd retained by the intravenously dosed animals rather than to greater endogenous cadmium excretion.

Miller et al. (1969) fed two groups of six male goats a diet with 100 µg Cd/g feed as $CdCl_2$ or a control diet for seven days before a single oral treatment of 500 µCi ^{109}Cd as cadmium chloride via a gelatin capsule. Feeding 100 µg Cd/g feed did not have an obvious effect on the excretion pattern. The daily rate of ^{109}Cd fecal excretion declined linearly and rapidly following the second week with about 20% of the body burden eliminated on day eight and less than 5% on day 14. This experiment could not differentiate which changes in excretion rate represent endogenous excretion from body organs versus gastrointestinal tract losses. However, when results are interpreted in light of parenteral studies, most of the cadmium excreted appears to come from the gastrointestinal tract.

Biliary excretion of cadmium after a parenteral dose is initially substantial (0.23% to 9%) and then rapidly levels off (Klaassen and Kotsonis 1977). Biliary excretion is dependent on the dose of cadmium administered; a higher cadmium dose results in a higher relative excretion. Elinder and Pannone (1979) reported the relative biliary excretion of cadmium (0.015% of body burden/day) to be higher than the urinary excretion (0.001%) but less than the total fecal elimination (0.034%) in rats receiving subcutaneous injections of cadmium. Klaassen (1978) has also assessed the role of metallothionein on plasma disappearance and biliary excretion of cadmium. When adult male Sprague-Dawley rats were given $^{109}CdCl_2$ (1.0 mg Cd/kg, intravenously) two days after induction of metallothionein (via 0.25 mg Cd/kg subcutaneously as cadmium chloride every other day for one week), the biliary excretion of cadmium decreased by more than 99%. Thus, it appears that once the cadmium is bound to metallothionein it is unavailable for excretion into the bile.

The parotid gland and the pancreas accumulate cadmium but their possible role in cadmium excretion has not been thoroughly investigated (Berlin and Ullberg 1963). Cadmium is secreted in saliva (Dreizen et al. 1970). However, cadmium was detected in 45% (13 of 29) and 100% (30 of 30) marmoset saliva samples obtained with pilocarpine and mecholyl as salivary stimulants, respectively. Small amounts of cadmium accumulate (<1% of total excretion) in the hair of experimental animals (Nordberg and Nishiyama 1972).

Cadmium excretion via milk is low. Tanaka et al. (1972) administered a single intravenous injection of 50 µCi of ^{115m}Cd as cadmium chloride (15 µg Cd) to pregnant ICR mice, 24 to 36 hours before delivery. No radiolabeled cadmium was administered to pregnant controls. In newborns, only 0.09% of the administered dose was detected, i.e., the amount excreted via the placenta. The cadmium concentration in milk of treated or control dams was not measured. Sucklings from the control group (not given radiolabeled cadmium) were suckled by the treated dams. Whole-body radiation measurements of the sucklings (born by controls and suckled by treated dams) after 14 days showed 0.31% of the maternally administered cadmium dose was detected in these sucklings. Cadmium transferred via lactation accounted for a larger portion of total cadmium transmitted to offspring than did transplacental transfer. This implies that only approximately 0.31% of cadmium administered to the dams was excreted in milk within 14 days.

2. Human Studies

Cadmium is excreted mainly via the urine in humans. In normal unexposed adults, the daily amount of cadmium excreted in the urine is about 1 to 2 µg/day. Some studies reveal a correlation between age, total body burden, and urinary cadmium concentrations. Urinary excretion of cadmium in exposed workers has been extensively documented (values range from zero to about 1000 µg/day) with the average value generally greater than in nonoccupationally exposed persons (Friberg et al. 1974).

Imbus et al. (1963) measured blood and urine cadmium concentrations in 154 healthy American men employed in 18 different types of industries, none of which involved work with cadmium. They reported the urinary cadmium concentrations (µg/L) as follows: mean = 1.59, median = 1.15, range = 0.5 to 10.8, 95th percentile = 4.13. Miller et al. (1976) measured cadmium concentrations in the urine of Australian men without a known occupational exposure to cadmium or lead (22 subjects in Group 1) and in a group with occupational exposure to lead (76 subjects in Group 2). Group 1 had a mean urinary excretion of 1.1 µg Cd/L (range: <0.5 to 2.5 µg/L) and group 2 had 2.0 µg Cd/L (range: <0.5 to 8 µg/L).

Ogata et al. (1980) obtained urine samples from 20 to 60 year-old Japanese subjects and reported mean cadmium concentrations (μg/L) by age group: 10 to 19 years had 0.396; 20 to 29 years had 1.102; 30 to 39 years had 1.161; 40 to 49 years had 1.327; 50 to 59 years had 1.959; 60 to 69 years had 2.483. In most age groups, females had higher mean urinary cadmium concentrations than males. Bernard et al. (1979) reported urinary cadmium concentrations of 0.82 μg/g creatinine in a control group of 77 workers and 11.4 μg/g creatinine in a group of 44 cadmium plant workers in Belgium. Ellis et al. (1980, 1981a) reported values for similar exposure groups.

Nogawa et al. (1980) measured urinary cadmium concentrations in subjects more than 40 years of age living in a nonpolluted (control) and a cadmium-polluted area of Japan. They reported mean concentrations of 4.8 ± 0.5 and 10.0 ± 1.93 mg Cd/g creatinine for 22 men and 20 women in the control group and 25.6 ± 2.57 and 36.7 ± 3.42 μg Cd/g creatinine for 34 men and 38 women inhabitants of the cadmium polluted area.

Roels et al. (1981a) collected urine (over a six hour period) from women more than 60 years of age who lived in a cadmium polluted area of Belgium (60 subjects) or in two less polluted regions (115 subjects) for most of their lives. None of the subjects had a history of diabetes or renal disease and their daily activities were normal for their age group. The women from the polluted city had 0.093 μg Cd/hour urinary excretion rates (range: 0.015 to 0.365) compared to rates of 0.055 μg Cd/hour (range: 0.012 to 0.119) and 0.040 μg Cd/hour (range: 0.002 to 0.156) in the two reference areas. The geometric means of the urinary excretion rates of cadmium for these three groups of older females are significantly different ($P<0.005$). Drinking water concentrations were not reported; however, airborne cadmium concentrations in the environment of each region reflect the urinary cadmium excretion rates.

Studies on exposed workers have not demonstrated a marked increase of urinary cadmium excretion as reported in animal studies. An increase in excreted cadmium is always accompanied by proteinuria but cadmium excretion has not been related to protein excretion. The evaluation of existing data is difficult since the status of subjects, i.e., body burden of cadmium, tubular dysfunction, acute illness or terminal illness, is often unclear. Clearly, further research is needed to reconcile the apparently contradictory results. *In vivo* determination of the kidney and liver burden may provide the most accurate estimates of exposure for these workers.

Lauwerys et al. (1976, 1979) formulated the following hypothesis to explain some of the contradictory biochemical data: at low exposures (ambient conditions) the amount of cadmium absorbed may be insufficient to saturate all the body binding sites (e.g. induced metallothionein) and urinary excretion does not increase proportionally to the magnitude of exposure. In these circumstances, the urinary cadmium concentration is principally in equilibrium with the body burden. At higher exposures (e.g., workers, adult Itai-Itai patients) and in the absence of renal lesions, the urinary cadmium concentration may closely reflect the magnitude of exposure (when all binding sites are saturated). Therefore, a latent period may be observed, in persons exposed for the first time, before urinary cadmium correlates with the magnitude of exposure. In these individuals, urinary cadmium values would accurately reflect the body burden of cadmium.

In humans, excretion of cadmium in feces (after absorption) is less important than urinary excretion. It is not known how much orally ingested cadmium is not absorbed and how much is actually excreted (CEC 1978). Tipton and Stewart (1970) reported that 30 to 50 μg Cd/day is excreted in the feces. Kowal et al. (1979) observed less than 18 μg/day in the feces.

Few reports exist on cadmium in bile and biliary excretion of cadmium in humans. Two studies based on bile samples collected during surgery found average cadmium concentrations of 1.1 ng/g and 2.0 ng/g, respectively (Elinder and Pannone 1979). Cadmium may also be excreted in saliva with concentrations up to 10 μg% (0.1 μg/g) (Dreizen et al. 1970). Several reports on cadmium concentrations in human hair have been published (mean concentrations from 0.44 to 3.5 μg/g) but with equivocal results relating magnitude of exposure to cadmium concentration (Friberg et al. 1974). Hair cadmium has been found to be highly variable in individual workers. Studies by Ellis et al. (1981b) have shown that hair cadmium concentrations are not a good index of body burden of cadmium in the industrially exposed individuals. Cadmium is absorbed onto hair and may be difficult to remove prior to analysis. Cadmium has also been detected in the saliva of occupationally exposed workers (mean values of approximately 60 μg/L) as well as those with no known occupational exposure (mean values of approximately 10 μg/L) (Gervais et al. 1981).

E. Bioaccumulation and Retention

1. Animal Studies

The biological half-time is an important factor in the toxicokinetics of cadmium. Animal experiments have shown highly variable results, in part, due to differences in dose, route of administration, duration of exposure, selected observation periods, etc. Some estimates of biological half-time values for experimental animals include: about 50 days for mice (Nordberg and Nishiyama 1972); 200 days for rats (Durbin et al. 1957); and 260 to 500 days for dogs (Burch and Walsh 1959). The values for biological half-times of cadmium are probably only valid prior to onset of renal damage. If renal tubular dysfunction develops, the excretion of cadmium will increase and, thus, changes in the biological half-time can be expected.

2. Human Studies

Information on biological half-times of cadmium in humans, as measured by decrease in retention of cadmium in an organ or whole-body, is scarce. The average cadmium excretion in a living population has been compared with average body burden based on autopsy data, as seen in Table III-15. Since urine is considered the major excretion route for body burden and 0.004% to 0.015% of the body burden is excreted daily, estimates of biological half-time for human beings range from 19 to 38 years. Ellis et al. (1979) estimated the biological half-time of cadmium for the whole body ranges from 10 to 33 years

Table III-15 Average Excretion in a Living Population Compared to Average Body Burden Based on Autopsy Data

Country	Body burden mg Cd	Urinary excretion[a] μg Cd/L	Body burden excreted daily %	Reference
Japan[b]	45-55	1.5-2	0.004-0.006	Tsuchiya et al. (1972)
USA[b]	15-20	1.6	0.012-0.015	Imbus et al. (1963), Friberg et al. (1974)
USA[c]	~19.3	1.7	0.013	Ellis et al. (1979)

[a] Assuming urine volume = 1.5 L/day.
[b] Autopsy data.
[c] *In vivo* data.

(average: 15.7 years) based on partial body in vivo neutron activation analysis. Hammer and Finklea performed theoretical calculations using mathematical models and estimated half-times of 9 to 18 years (Friberg 1974). Travis and Haddock (1980) using a single compartment model predicted an age-dependent biological half-time ranging from 34 to 11 years with increasing age.

F. Summary

Orally ingested cadmium salts are not rapidly absorbed from the gastrointestinal tract of animals or humans. Typically, most of an oral dose of cadmium remains in the gastrointestinal tract and is excreted in the feces within three to six days. The amount of cadmium absorbed is rather variable, but is generally 1% to 5% of the ingested dose. A number of factors are recognized which influence cadmium absorption, including: (1) age (young mice absorb four to eight times more of an oral dose than do older mice); (2) Ca^{2+} status (low Ca^{2+} diets or elevated vitamin D levels promote increased absorption); (3) exposure history (absorption of an oral dose of cadmium increased two-fold in mice receiving 75 mg Cd/L in drinking water for two weeks); (4) diet (low protein diets and diets low in zinc, iron or copper promote increased absorption); (5) sex (females absorb more than males); and (6) pregnancy (increased absorption in mice occurs during gestation and lactation). Absorption of cadmium inhaled into the lungs is difficult to measure precisely (estimates range from 40% to 96%), but is much higher than gastrointestinal absorption. Cigarette smoke may be a significant source of inhaled cadmium and several studies have shown elevated cadmium concentrations in blood and tissue of smokers compared to non-smokers.

Cadmium which is absorbed distributes to all tissues of the body, but there is clear preferential accumulation in liver and kidney. For example, a single oral dose of $^{109}CdCl_2$ given to goats was found after two weeks to be present in hair, skin, testes, bone, muscle, heart, lung, pancreas and spleen at levels of 0.001% to 0.060% dose/kg tissue, while levels were 0.59% to 0.63%/kg in liver, and 1.13% to 1.69%/kg in kidney. Similar results are observed after chronic ingestion of cadmium. In monkeys or dogs receiving ^{109}Cd once per month for 14 months, radioactivity was found in brain, heart, lung, spleen, testes, muscle and bone in concentrations from 0.01% to 0.06% total body radioactivity/g tissue, while concentrations in liver were 0.10% to 0.31%/g, and concentrations in kidney were 0.51% to 1.24%/g tissue. Of the total body radioactivity, 37% to 39% was found in liver and 38% was found in kidney, the remainder being spread throughout the body. Rats receiving 200 mg/L $CdCl_2$ in their drinking water for 18 months showed blood concentrations of 18 μg/dL blood, but liver and kidney concentrations of 250 to 260 μg/g wet tissue.

Numerous studies of cadmium concentrations in human autopsy tissue have been performed. While there is considerable variation among individuals and between different geographic areas, the distribution pattern observed in animals is also found in humans. In a study in Japan, tissues such as brain, lung, heart, spleen, intestine, gonads, muscle, skin and bone, cadmium concentrations ranged from 0.1 to 1.2 μg Cd/g wet tissue, while concentrations in liver were 3.2 to 8.1 μg/g tissue, and in kidney 36 to 58 μg/g tissue. Tissue levels were higher in females than males. Of the total body burden (mean value: 35 mg Cd), an average of 11.7 mg (33%) was found in kidney and 8.5 mg (24%) was found in liver.

Cadmium ion is not itself subject to metabolic transformation in the body. However, cadmium absorption and distribution are influenced by the presence of metallothionein, a small (molecular weight about 6,000) binding protein found in blood and most tissues. The function of this protein is not clear, but its synthesis is increased by exposure to cadmium. When cadmium is administered to rats as the Cd-metallothionein complex (either by injection or by oral feeding), accumulation in the kidney is markedly increased, suggesting that renal reabsorption of the complex is more efficient than for free cadmium. Since cadmium ingestion results in increased concentrations of metallothionein (or a similar protein) in plasma, this may in part explain renal accumulation of cadmium. Several authors have found a correlation between cadmium exposure and urinary metallothionein concentration in humans and have suggested that this may be a more useful indicator of chronic cadmium exposure than plasma cadmium levels.

Absorbed cadmium is not rapidly excreted from the body. In animals, most cadmium excretion occurs via the urine at rates ranging from 0.01% to 1% of the total body burden per day. Similar values are obtained in humans, where typical urinary loss of cadmium is only 1 to 2 μg/day. Urinary cadmium levels increase following cadmium exposure, but there is no strict relationship between exposure level and urinary cadmium concentration, suggesting that this may not be the best indicator of exposure. Fecal excretion of absorbed cadmium occurs in both animals and humans, but again the rate is low (0.03% to 0.1% total body burden per day). Fecal excretion tends to decrease after cadmium exposure, while urinary excretion remains more constant. Excretion via sweat and saliva occurs, but is quantitatively less important. Accumulation of cadmium in hair is difficult to measure since cadmium adsorbs onto hair and is not easily removed.

Slow excretion of cadmium is synonymous with long half-times in the body. There is considerable variation in the estimates of cadmium half-times, but some representative values are: 50 days in mice, 200 days in rats, 260 to 500 days in dogs, and from 10 to 38 years in humans. When renal injury occurs, urinary cadmium excretion may increase.

Because cadmium excretion is so slow, cadmium is readily accumulated in the body. In rats ingesting 200 mg/L $CdCl_2$ in water, tissue levels rose from 0.3 to 260 µg/g in liver and from 0.5 to 250 µg/g in kidney after 11 months of exposure. In humans, there is an age-dependent accumulation in liver and kidney, reaching a maximum at age 50 to 59. After this, tissue levels decreased. The total human body burden of cadmium at birth has been estimated to be about 0.1 mg and this increases to about 15 to 30 mg by adulthood in persons on a North American diet.

IV. HUMAN EXPOSURE

Humans may be exposed to cadmium in drinking water, food and air. Detailed information concerning the occurrence of and exposure to cadmium in the environment is presented in another document entitled, "Occurrence of Cadmium in Drinking Water, Food and Air" (Letkiewicz et al. 1984). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

A. Exposure Estimation

This analysis is limited to drinking water, food and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to cadmium from sources other than the three considered here. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works and travels, what one eats and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various cadmium concentrations. The 70-kg human is used for estimating intake.

1. Drinking Water

There are very limited data available for characterizing human intake of cadmium from drinking water provided by public water supplies. Based on the data presented in Letkiewicz et al. (1984), it appears that the drinking water delivered to most (over 90%) of the approximately 214 million people in the United States using public water supplies does not have cadmium present above 2 μg/L. Based on the compliance monitoring data presented in the Federal Reporting Data System (FRDS 1984), it can be estimated that approximately 60,000 people receive drinking water with cadmium levels above 10 μg/L, the current MCL. While all but 4 of the 25 individual supplies with levels above 10 μg/L have a groundwater source, over 84% of the exposed population (50,250 people) are exposed from the four surface water sources; almost 60% (35,000 people) are exposed from one of the surface water sources.

The data available are too limited to develop a reliable profile of human exposure to various levels of cadmium in drinking water below the current MCL.

2. Diet

Several estimates of dietary intake of cadmium in the United States have been reported for recent years. The Food and Drug Administration (FDA) includes cadmium among the contaminants analyzed for in its Total Diet Studies ("Market Basket Surveys"). Table IV-1 presents the daily intake estimates for the adult male for several years as reported in recently published Total Diet Studies (FDA 1980, 1982). As shown in Table IV-1, cadmium intake from food has remained relatively unchanged over the six years for which data are provided.

Data obtained in the 1979 Total Diet Study for the adult male (FDA 1982) indicated that cadmium was present in all 12 of the food groups categorized by FDA. Sixty-eight percent of the total intake came from three of the food categories: grain and cereal (30.9%), potatoes (20.7%) and beverages (16.4%).

3. Air

There are few published estimates of the respiratory intake of cadmium. The ICRP (1974) indicates that total airborne cadmium intake for the reference man is less than 1 µg/day. This level of intake is also suggested by the ambient air measurements presented in Section 4 (Occurrence in Ambient Air) of Letkiewicz et al. (1984). Using a typical median value of 0.007 $\mu g/m^3$ from the USEPA National Air Surveillance Networks (NASN), data presented in Letkiewicz et al. (1984), and assuming an adult male inhales 23 m^3 of air/day, the average intake for the adult male would be 0.16 µg/day. No information was obtained on the absorption rate of inhaled cadmium.

Table IV-1 Summary of FDA Total Diet Study Estimates for Cadmium Intake for the Adult Male

Fiscal year	Intake (μg/day)
1979	32.6
1978	30.9
1977	36.9
1976	32.9
1975	34.0
1974	33.5

Adapted from FDA (1980, 1982).

B. Summary

There is a very limited data base on human exposure to cadmium from drinking water, food and air. While some information is available to suggest the general range of cadmium intake from these media, it is not possible to determine what proportions of the population have drinking water, dietary and respiratory intakes at various levels. For drinking water, it is possible to estimate the size of the population exposed to levels in public water supplies above 10 µg/L, the current MCL, but not for various levels at or below 10 µg/L. Consequently, a detailed relative source contribution assessment that describes the importance of each medium as a cadmium source for different segments of the U.S. population could not be developed.

While it is not possible to develop a detailed profile of human exposure to cadmium and the relative source contributions from the three media of interest, it is possible to illustrate the relative importance of each source for various assumed exposure conditions. Table IV-2 presents an illustrative relative source contribution assessment for cadmium for the adult male. The intake values for air and food shown in Table IV-2 are based on the typical intakes presented in Section IV.A (Exposure Estimation) above. Six separate intake levels for drinking water, one intake level for food and one for air are presented in Table IV-2.

The calculations shown in Table IV-2 suggest that for the adult male, food is generally the predominant source, accounting for about 60% of the total

Table IV-2 Relative Source Contribution Assessment for Cadmium for the 70-kg Adult Male

		Food intake: 0.41 µg/kg/day[a]; Air intake: 0.002 µg/kg/day[b]			
Drinking water concentration (µg/L)	Drinking water intake[c] (µg/kg/day)	Food intake (µg/kg/day)	Air intake (µg/kg/day)	Total intake (µg/kg/day)	% from drinking water
0	0	0.41	0.002	0.41	0
2	0.06	0.41	0.002	0.47	12
5	0.14	0.41	0.002	0.55	25
10	0.29	0.41	0.002	0.70	41
20	0.57	0.41	0.002	0.98	58
40	1.14	0.41	0.002	1.5	73

[a] The intake for food is derived from the FDA Total Diet Studies indicating dietary intake for the adult male to be about 33 µg/day. Since some portion of this FDA value comes from drinking water consumed as tap water and used in the preparation of other products, an adjustment was made in the dietary intake value to account for the drinking water contribution. This adjustment assumes a typical drinking water level of 2 µg/L and a total consumption of two liters/day. Therefore, it is assumed here that the non-drinking water dietary intake is 29 µg/day, or 0.41 µg/kg/day, for the 70-kg adult male.

[b] Based on an estimated air intake of 0.16 µg/day (which corresponds to 0.007 µg/m^3).

[c] Assumes consumption of two liters/day.

intake for individuals exposed to drinking water with cadmium levels below 10 µg/L. This appears to be the majority of the population. Drinking water significantly exceeds food as the predominant source of exposure for the adult male only at levels of 20 µg/L or greater, which is twice the current MCL.

V. HEALTH EFFECTS IN ANIMALS

Cadmium has no known biological function but is toxic to mammals. It has been shown to have mutagenic, teratogenic, and carcinogenic effects. Cadmium exposure results in a variety of acute and chronic effects; most notably renal tubular damage and hypertension. Cadmium is an extremely toxic metal, but results from acute studies have only limited value on predicting effects produced by long-term (chronic) oral exposure to cadmium; thus, the following discussion will emphasize the more relevant chronic studies.

A. General Toxicity

The acute oral LD_{50}s of cadmium compounds for various animal species are listed in Table V-1. Depending on the chemical form, the oral LD_{50} in rats varies from 16 to >5,000 mg/kg.

B. Target Organ Toxicity

1. Nervous System Effects

Large parenteral doses of cadmium are toxic to ganglia. Gabbiani et al. (1967) administered 10 mg/kg of cadmium as $CdCl_2$ subcutaneously to guinea pigs, golden hamsters, mice and Sprague-Dawley rats (ten/group) (age not specified) and four days later observed hemorrhagic lesions of the gasserian and sensory spinal ganglia. The lesions were characterized by hemorrhagic

Table V-1 Acute Oral LD_{50} of Cadmium Compounds in Animals

Compound	Species	LD_{50} (mg/kg)
Cadmium acetate	Rat	333
Cadmium bromide	Rat	322
Cadmium chloride	Rat	88-302
	Guinea pig	63
	Mouse	5-175
Cadmium carbonate	Rat	438-659
Cadmium cyanide	Rat	16
Cadmium fluoroborate	Rat	250
Cadmium fluoride	Guinea pig	150
Cadmium fluorosilicate	Rat	100
Cadmium formate	Rat	162
Cadmium iodide	Rat	222
Cadmium nitrate	Rat	397
Cadmium oxide	Rat	72-296
Cadmium perchlorate	Rat	875
Cadmium (metal) powder	Rat	2,330
Cadmium propionate	Rat	300
Cadmium selenide	Rat	>5,000
Cadmium stearate	Rat	1,225
Cadmium succinate	Rat	660
Cadmium sulphate	Rat	357
Cadmium sulphide	Rat	>5,000

Adapted from Christensen and Luginbyhl (1974), Mego and Cain (1975), Yoshikowa and Ohsawa (1975), CEC (1978).

suffusions around ganglion cells, several of which exhibited karyorrhexis or nuclear pycnosis with lysis of the cytoplasm. Pretreatment with zinc acetate (44 mg/animal, subcutaneously) or glutathione (150 mg/animal, iv) reduced the cadmium induced neurotoxicity.

2. Kidney Effects

Many experiments on kidney function in animals have not investigated low molecular weight protein excretion; yet, it is known that histological changes may not be found when moderate proteinuria is already present. This fact may cast doubt on conclusions, particularly those regarding threshold limits, drawn from animal experiments in which specific urinary proteins were not measured (CEC 1978).

Subcutaneous injections of $CdCl_2$ (9 to 10 mg Cd/kg) in rats and rabbits produced renal tubular damage (Foster and Cameron 1963). Bernard et al. (1978) administered 1 mg Cd/kg (as $CdCl_2$) intraperitoneally to twenty-two-month-old female Sprague-Dawley rats five-times-a-week for three months. After two months, the cadmium-treated rats exhibited significantly increased mean proteinuria (1500 mg/g creatinine) relative to controls (510 mg/g creatinine) as well as increased aminoaciduria (490 mg α-nitrogen/g creatinine versus control rats with 356 mg α-nitrogen/g creatinine). The profile of urinary proteins remained unchanged in the cadmium-treated rats until the third month of treatment when the mean cadmium concentration in the renal cortex of treated rats was 230 μg/g (wet weight) versus 0.17 μg/g in control rats. The experimentally induced proteinuria in rats, as analyzed by electrophoresis or gel filtration, was similar to that observed in humans occupationally exposed to cadmium. In the chromatograms from all cadmium-treated rats, the more quantitatively important peaks were found in the high molecular weight fractions. Generally, the major peak had an electrophoretic mobility and elution volume corresponding to albumin. This peak was preceded by peaks corresponding to transferrin and IgG. In the low molecular weight fractions, the major peak corresponded to retinol binding protein followed by smaller peaks containing β-microglobulin and post-γ-protein. Alpha$_1$-microglobulin was eluted between albumin and retinol binding protein. The authors suggest these data strengthen the hypothesis that cadmium-induced proteinuria is a mixed type proteinuria involving not only the tubule but also the glomerulus.

Nordberg and Piscator (1972) administered cadmium as $CdCl_2$, (0.25 or 0.5 mg Cd/kg/day) via subcutaneous injections to adult male CBA-mice for 25 weeks. Pathologic electrophoretic patterns with a prominent β peak in the high dose group were observed during the last month of the study. Urinalysis revealed negligible excretion of cadmium during the initial weeks of the experiment and a sharp increase appearing simultaneously with pathologic patterns in the urine electrophoresis. Urinary cadmium appeared to be bound to metallothionein. However, the investigators found a decrease in total protein excretion from the fourth week of treatment for both dose groups. Although decreased proteinuria in cadmium-dosed mice may result from an effect on (1) liver synthesis of the major urinary protein complex or (2) the excretion mechanism in the kidney, the authors suggest that the unexpected data result from altered testosterone production. Normal proteinuria in male mice originates mainly from the production of testosterone-dependent low molecular weight proteins in the liver and excretion of these proteins by the kidneys. Cadmium accumulates in the testicles and the hypophysis and may interfere with testosterone production at those sites.

Fowler et al. (1975) fed male Charles River rats (age not specified, 32 animals/dose group) 0, 0.2, 2, 20 or 200 mg Cd/L (approximately 0, 0.013, 0.13, 1.33 or 5.3 mg/kg/day, assuming 0.025 L/day for 0 to 20 mg Cd/L, 0.010 L/day for 200 mg Cd/L and a body weight of 0.375 kg)[a] as $CdCl_2$ via drinking water for 6 to 12 weeks. Half of the animals were fed a normal calcium (0.7%) diet and the remainder a low calcium (0.1%) diet. Light and electron microscopic analysis of kidney slices revealed constriction of the smaller renal arteries, mild dilation of larger arteries and a diffuse, dose-related scarring of peritubular capillaries. Smooth muscle cell necrosis was not observed. Arterial constriction was most marked at 6 weeks and appeared to subside by 12 weeks. Deposition of peritubular connective tissue fibers was most marked in the 12-week group. These observations were correlated with dose-dependent renal cadmium concentrations and significant increases in blood urea nitrogen (BUN) concentrations. This work implicates vascular changes in cadmium nephropathy. Some of the pertinent data from the six-week exposure animals are summarized in Table V-2. Kidneys of cadmium-exposed rats on the low calcium diet had a higher content of cadmium than those on the normal calcium diet.

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[a] Doses expressed as mg/kg/day in parentheses have been calculated from the published data and/or assumptions regarding body weight, exposure concentrations and water consumption. The calculated mg/kg/day values are not accurate because body weight and water consumption change over time, especially in long-term chronic studies. This effort to convert exposure concentrations to doses is done to provide approximate reference posts for future regulatory decision-making.

Kotsonis and Klaassen (1978) exposed 50- to 70-day-old Sprague Dawley male rats to cadmium (as $CdCl_2$) in drinking water at concentrations of 0, 10, 30 and 100 mg Cd/L (approximately 0, 0.84, 2.15, 6.44 mg/kg/day, based on reported mean daily water consumption of 0.0411, 0.0362 and 0.0282 L/day and body weights of 0.488, 0.506 and 0.438 kg) for 24 weeks. There were six to nine rats in each exposure group and a control group. Toxicity observed after six weeks of exposure included renal injury which was indicated by an increase ($P<0.05$) in urinary protein for rats receiving cadmium at concentrations of 30 and 100 mg/L (2.15 and 6.44 mg/kg/day), but no effects ($P>0.05$) were observed in rats receiving 10 mg/L (0.84 mg/kg/day) during the 24-week study.

Nishizumi (1972) conducted an electron microscopic study of cadmium nephrotoxicity in the rat. Three-month-old male Wistar King A rats were allowed free access to water containing 0, 10, 50 or 300 mg Cd/L (approximately 0, 0.45, 2.27, or 13.6 mg Cd/kg/day, assuming 0.014 L/day and a body weight of 0.300 kg) as $CdCl_2$. There were 8 rats in the control group and 12 rats in each Cd dose group. Two control and three experimental animals from each group were sacrificed after 6, 12, 24 and 40 weeks. Renal changes detected by electron microscopy were principally confined to the cells of the proximal tubules. An increase in lysosomes and swelling of mitochondria were the two

Table V-2 Dose-Related Effects of Cadmium on the Kidney

Cd dose in water (mg/L)	Mean daily Cd consumption (µg/rat)	Cd concentration in kidney (µg/g)	Average ID/TD ratio (%)[a]	Mean BUN[b]
0	-	1.13	48.6	14.7
0.2	5	0.64	44.9	16.0
2	50	2.40	44.5	14.0
20	500	9.03	40.4	18.5
200	2,000	28.24	42.7	23.5

[a] Internal (ID) and total (TD) diameters of small renal arteries (≤80 µm).
[b] Blood urea nitrogen (BUN).

Adapted from Fowler et al. (1975).

distinct histologic features. The size and number of lysosomes increased in proportion to the dose of ingested cadmium. The usual elongated, rod-shaped mitochondria of the proximal tubular cells became oval or rounded and increased in volume. The cristae were vesicular, shortened and marginal. Other changes noted were an increase of microbodies, focal proliferation of the smooth endoplasmic reticulum and appearance of intranuclear inclusions. The author considered these alterations in the proximal tubular cells to be indications of an activation of detoxifying processes and an impairment of energy metabolism. Table V-3 summarizes the morphologic events in proximal tubular cells relating to concentration and duration of cadmium exposure.

Coagulation necrosis, glomerular fibrosis and marked interstitial fibrosis were found in the renal cortex of rabbits that ingested 14.9 mg Cd/kg/day (as $CdCl_2$ in drinking water) for 200 days (Stowe et al. 1972). The proximal tubule epithelium contained apical cysts, dilated endoplasmic reticulum and degenerated nuclei. Renal enlargement was also observed.

Prigge (1978) fed female SPF Wistar rats (age not specified; 12/group) 0, 25, 50, and 100 mg/L cadmium (as $CdCl_2$) via drinking water for 90 days. This corresponded to doses of approximately 0, 3.0, 6.2 or 12.4 mg Cd/kg/day, assuming consumption of 0.028 L of water/day and body weights of 0.240, 0.231, 0.233 and 0.221 kg, respectively. At the same time, female Wistar rats, 170 to 190 g, were exposed to cadmium oxide aerosols (25 or 50 μg Cd/m^3 for 90 days or 100 $\mu g/m^3$ for 100 days; 12/group). While rats exposed to 25 to 100 μg cadmium oxide $aerosol/m^3$ exhibited no increase in protein

Table V-3 Summary of Morphologic Events in Proximal Tubular Cells

	Cadmium exposure[a]											
	10 mg/L				50 mg/L				300 mg/L			
Changes of organelles	6[b]	12	24	40	6[b]	12	24	40	6[b]	12	24	40
Aggregates of smooth membranes	+	+	++	++	++	++	+	+	++	++	+	+
Increase of microbodies	-	-	+	++	++	++	+	+	++	++	+	+
Mitochondrial changes	-	-	+	+	-	-	+	++	-	+	++	+++
Increased lysosomes	-	-	+	+	-	+	++	+++	-	+	+++	+++

[a] -, negative; +, slight; ++, moderate; +++, marked.
[b] Weeks of exposure.

Adapted from Nishizumi (1972).

excretion, there was significant protein loss in animals orally exposed to cadmium. The concentration of alkaline phosphatase in urine was not influenced by either route of cadmium administration. The urinary data from the rats exposed to cadmium via drinking water are summarized in Table V-4.

3. Liver Effects

Hata et al. (1980) demonstrated that strain differences within a given species may affect susceptibility to cadmium toxicity. They administered 30 µmol/kg of cadmium as $CdCl_2$ to male mice (42 to 51 days old) and found that zero of nine DBA/2, two of seven BALB/C and seven of nine C3H mice died within 48 hours. These findings correlated with marked hepatic histological changes in the C3H mice and little to no change in DBA/2 or BALB/C mice. The rate of metallothionein induction in liver was found to be significantly lower in C3H mice than in the other two strains. Piletz et al. (1983) have also examined this phenomenon. In this study C3H mice were more sensitive to cadmium-induced mortality (30 µmol Cd/kg) than DBA/2 mice. Further, DBA/2 mice accumulated more ^{109}Cd in hepatic metallothionein than C3H mice. Following a non-lethal dose of 8 µmol $CdCl_2$/kg, the rates of both synthesis and degradation of cadmium-induced metallothionein were higher in C3H mice than in DBA/2 mice.

Acute parenteral administration of lethal or near lethal doses of cadmium compounds may result in morphologic and functional changes in the liver of animals including necrosis and leakage of aminotransferase into the blood.

Table V-4 Summary of Urinary Protein and Alkaline Phosphatase Excretion in Rats Exposed to Cadmium

Cd concentration (mg/L)	Urinary protein (mg protein/mg creatinine)	Urinary alkaline phosphatase excretion (U/mg creatinine)
0	5.94±1.66	0.387±0.177
25	7.28±1.08	0.284±0.123
50	8.00±1.01[a]	0.327±0.117
100	10.13±1.63[a]	0.327±0.128

[a] $P<0.05$.

Adapted from Prigge (1978).

Single intraperitoneal injections of cadmium (0.84 mg Cd/kg) will alter liver microsomal enzyme activity causing changes in drug metabolism (Johnston et al. 1975). Pretreatment with zinc acetate (4 mg Zn/kg) or sodium selenite (1.6 mg Se/kg) ameliorates the cadmium-induced inhibition in drug metabolism (Early and Schnell 1978, 1981).

Stowe et al. (1972) fed male Flemish Giant and New Zealand White rabbits (five per strain, three-months-old), 160 mg Cd/L (as $CdCl_2$) of drinking water for 200 days. An equal number of similar animals received untreated drinking water. The cadmium-exposed rabbits consumed an average of 14.9 mg Cd/kg/day. Light microscopic examination of liver tissue revealed that test animals were generally devoid of glycogen and had varying degrees of periportal and interlobular collagen deposition. Inflammatory cell infiltrates in the portal regions and biliary hyperplasia were frequently observed. Electron microscopic examination of liver tissue demonstrated a marked increase in smooth endoplasmic reticulum, especially in the periphery of cells. There was also prominent dilatation of the rough endoplasmic reticulum, a relative absence of glycogen granules and a deposition of collagen, particularly in perilobular and periportal areas. The following clinical signs from liver function tests were unaffected by cadmium toxicity and showed no strain specificities when cadmium concentrations reached 188 μg/g wet weight: serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bromsulfophthalein retention, lactic dehydrogenase isoenzymes (1 through 5), clotting time, prothrombin time, and partial thromboplastin time.

Sporn et al. (1970) examined the influence of cadmium on carbohydrate and cellular energy (ATP) metabolism in the liver. Cadmium chloride was administered to groups of eight Wistar rats (three to four weeks old, sex not specified) via drinking water (1 mg Cd/L) or via food (1, 10 or 25 µg Cd/g feed). The results indicated cadmium interference in carbohydrate metabolism at the glycogen splitting level (increased phosphorylase a activity) and on the Embden-Meyerhof pathway (decreased aldolase activity). Cadmium did not alter the pentose phosphate shunt (G6PDH activity). Cadmium did influence cellular energy (ATP) metabolism (decreased P/O ratio due to lower P concentration without modified O_2 uptake) although cytochrome oxidase activity was not altered. No alterations in activity of blood catalase, glutamic-pyruvate transaminase, uricase or acid and alkaline phosphatase were noted. Pertinent data (means) are summarized in Table V-5. In other experiments Sporn found that 10 ppm cadmium as $CdCl_2$ administered orally for 60 days inhibited succinic oxidase activity.

Miller et al. (1974) performed a morphometric analysis of liver parenchymal cells on weanling male Sprague-Dawley rats fed laboratory chow or semipurified diets (two to six/group). Cadmium (as $CdCl_2$) was administered in the drinking water at 17.2 mg/L for 71 and 280 days. Two concentrations of copper and zinc were given in the semipurified diets: (1) 0.25 mg Cu/L and 2.5 mg Zn/L and; (2) 1.0 mg Cu/L and 10 mg Zn/L. Endoplasmic reticula were grossly altered by the presence of cadmium. Nodules of densely packed tubular smooth endoplasmic reticulum were found in many cells. The nodules were prominent and appeared in close proximity to mitochondria at 71 days and

Table V-5 Influence of Cadmium Administration on Carbohydrate and Cellular Energy (ATP) Metabolism in the Rat Liver

Cadmium concentration (mg/L)	Duration (days)	Dose Cd ingested (mg)	P_i (µmol)	O (µatmos)	P/O ratio	Phosphorylase a (µmol P_i/g wet wt/min)	Phosphorylase b (µmol P_i/g wet wt/min)	Aldolase (µmol Fru-1,6-P_2/g wet wt/hr)
0	42	0	--	--	--	--	--	691
0	60	0	11.8	5.5	2.14	26	207	863
0	335	0	13.9	7.3	1.89	33	288	754
1	42	0.6	--	--	--	--	--	548
1	335	4.2	15.4	7.7	2.03	40	240	574
10	42	5.0	--	--	--	--	--	530
10	60	9.2	8.8	5.1	1.73	46	170	565
25	42	14.0	--	--	--	--	--	507

Adapted from Sporn et al. (1970).

increased in number at 280 days. The total endoplasmic reticulum was elevated from 6.18 to 6.53 μ^2/μ^3 after 71 days of cadmium and to 7.72 μ^2/μ^3 at 280 days. Volume density of smooth endoplasmic reticulum increased in the group treated with cadmium for 71 days from 20.9% to 23.7% and from 20.8% to 28.9% in the group treated for 280 days. Rough endoplasmic reticulum volume density decreased after cadmium administration from 13.5% to 11.1% and from 13.1% to 8.2% in the treated groups after 71 and 280 days, respectively. Membrane-bound ribosomes appeared in spirals and rosettes although they were not closely packed. Junctions of rough and smooth endoplasmic reticulum with sites of degranulation of ribosomes were frequently observed. Glycogen quantities were diminished. Cadmium appeared to cause no change in mitochondrial volume density but cup-shaped figures and other forms with unusual longitudinally oriented cristae were common. Hepatocytes from rats fed the semipurified diet with low copper and zinc plus cadmium demonstrated a significant increase in smooth endoplasmic reticulum compared to animals receiving adequate levels of the metals. This study showed that the activity of cadmium was critically influenced by the nutritional status of the animal, i.e., the essential metals for which cadmium may be an antagonist.

4. Bone Effects

Cadmium can induce bone lesions in animals. Larsson and Piscator (1971) examined the effect of 25 mg Cd/L (approximately 2.10 mg/kg/day, assuming 0.028 L/day and a body weight of 0.333 kg) administered via drinking water to eight-month-old Sprague-Dawley rats (sex not specified). Rats were maintained on low or normal calcium diets for one or two months (five to six/group). The content of inorganic matter in the tibia decreased by 5.7% and 7.5% in the animals on the reduced calcium diet for one and two months, respectively. The decrease of inorganic matter in the bone corresponded to an increase in water content with unchanged organic matter, indicating osteoporosis. The authors suggested that the osteoporosis, seen after two months, resulted from increased bone resorption which mobilized skeletal calcium to maintain calcium in the blood. Data obtained from the right tibia of tested rats (summarized in Table V-6) indicate that the calcium deficient diet is the primary factor for the bone disease.

Itokawa et al. (1973) divided 40 male Wistar rats (age not specified) into eight groups of five animals and administered various diets, high or low in concentrations of protein (20% or 5% casein), calcium (1.82% or 0%) and cadmium chloride (0% or 0.04%). The most striking roetgenographic finding was abnormal curvature of the spinal column. Cervicodorsal lordosis and dorsolumbar kyphosis and scoliosis increased markedly in rats fed a low-protein, calcium-deficient diet with cadmium. Cadmium concentrations approximately doubled and magnesium and zinc concentrations decreased significantly in cervical and lumbar vertebrae and femurs of cadmium-treated rats.

In a follow-up study, Itokawa et al. (1974) fed male Wistar rats (groups of five, age not specified) calcium adequate (1.82% of diet) or deficient (0% of diet) chow and 50 mg Cd/L as $CdCl_2$ via drinking water for 120 days. In the

Table V-6 The Concentrations of Water, Organic and Inorganic Matter, and Calcium Accretion Rate in Rats Treated with Cadmium and Diets Adequate or Deficient in Calcium

Duration	Group	Water % wet weight	Organic matter % wet weight	Inorganic matter % wet weight	Ca accretion rate mg Ca/hr x 10^{-7}
1 month	25 mg Cd/L + 1.0% Ca	26.48	27.31	46.21	1.95
	25 mg Cd/L + 0.04% Ca	28.45	28.38	43.15	2.19
	0 mg Cd/L + 0.04% Ca	28.13	27.89	43.98	2.29
	0 mg Cd/L + 1.0% Ca	25.08	28.14	46.78	2.17
2 month	25 mg Cd/L + 1.0%Ca	24.37	27.97	47.67	2.12
	25 mg Cd/L + 0.04% Ca	27.34	28.27	44.40	2.40
	0 mg Cd/L + 0.04% Ca	25.16	27.73	47.12	2.46
	0 mg Cd/L + 1.0% Ca	24.50	27.49	48.01	2.16

Adapted from Larsson and Piscator (1971).

femurs, thinning of cortical osseous tissue, slight decrease in osteocytes, decrease in acid mucopolysaccharides in epiphyseal cartilage and appearance of osteoid plus fat deposition in bone marrow were significant in calcium-deficient cadmium-treated rats (approximately 3.78 mg/kg/day, based on reported value of 0.66 mg Cd/day and assuming a body weight of 0.175 kg). Some data from the analysis of femurs are presented in Table V-7. In this long-term, low-level cadmium study, the spinal column remained intact. In another study, Itokawa et al. (1978) confirmed these findings and correlated them with functional and histological changes in the kidneys.

Takashima et al. (1980) observed osteomalacic changes in male Wistar rats (age not specified, six to seven/group) fed cadmium as $CdCl_2$ at various dietary concentrations for 19 months. Evidence of osteoid tissue containing glycoaminoglycans and collagenous tissue was obtained histologically. Dose-dependent increases in fat tissue replacement of bone marrow, irregularity of the columnar structure of the cartilage plate, irregularity of thickness of cortical osseous tissues and osteoid in cortical osseous tissues were observed. Concentrations of selected minerals in the femurs of rats are presented in Table V-8.

Similar results were obtained by Yuhas et al. (1979) using 28-day-old male Sprague-Dawley rats. Groups of six rats ingested 1, 10 or 100 mg Cd/L (approximately 0.096, 0.78, 6.6 mg/kg/day, based on reported values of 0.409, 0.033, 0.028 L/day respectively and assuming a body weight of 0.425 kg) of drinking water containing cadmium acetate for 13 weeks.

Table V-7 Femur Weight and Cadmium, Calcium, Magnesium, Zinc and Phosphorus Levels in Cadmium-Treated, Calcium-Deficient Rats

Group	Cd in H_2O (mg/L)	Femur (g)	In bone (level per 100 g dry weight) Cd (mg)	Ca (g)	Mg (mg)	Zn (mg)	P (g)
Ca adequate	-	1.07	0.19	24.0	437	27.0	10.7
Ca deficient	-	0.80	0.21	15.2	435	27.1	6.7
Ca adequate	50	0.76	1.00	22.6	448	25.0	9.3
Ca deficient	50	0.56	1.94	16.8	407	26.6	7.1

Adapted from Itokawa (1974).

Table V-8 Concentrations of Various Minerals in Femurs

Amount Cd in diet	Ca mg/g	Cd µg/g	Zn µg/g	Fe µg/g	Mg µg/g	Cu µg/g	Na mg/g
0 mg/L	156.7	1.07	118.1	49.1	2.31	2.17	4.78
10 mg/L	147.5	1.17	112.2	42.3	2.23	2.40	4.23
50 mg/L	144.8[a]	3.09[a]	105.1[a]	36.4[a]	2.15	1.82	4.01[a]
100 mg/L	143.6[a]	4.60[a]	100.3[a]	33.2[a]	2.32	2.06	3.70[a]

[a] $P<0.05$

Adapted from Takashima et al. (1980).

Nogawa et al. (1981) showed that cadmium can produce osteomalacia similar to that observed under conditions of inadequate vitamin D intake. Female Wistar rats (four to six/group, age not specified) were fed cadmium chloride (10 mg Cd/100 g of chow) for 500 days. The chow was either vitamin D adequate, slightly deficient or totally deficient (0, 1 and 5 IU/100 g). The results clearly demonstrated that chronic cadmium exposure can induce the same reactions in bone and plasma as those observed in animals with vitamin D deficiency. In the cadmium-treated animals, the vitamin D-adequate group showed the same changes in bones and plasma as those of the vitamin D-deficient control group. The principal findings were: abnormal osteoplasia with osteoid tissue formation; marked degeneration in renal tubules; decreased amount of calcium in bones; decreased plasma-calcium levels; and increased urinary excretion of total protein, lysozyme and calcium. These findings suggest that cadmium-induced bone disease is closely related to renal tubular dysfunctions.

Miyahara et al. (1983) studied the toxic effect of cadmium on bone using a cultured chick embryo bone preparation. They found that cadmium (8.9 μM) decreased collagen content, decreased mineral (calcium) content and inhibited the activity of alkaline phosphatase. Concomitant addition of zinc prevented the decrease in collagen and inhibition of alkaline phosphate but not the decrease in mineral content. The cadmium content in bone was increased by zinc treatment, but most of the cadmium was sequestered in metallothionein. The authors concluded that zinc-induced metallothionein served as a cadmium scavenger and contributed to the protection against cadmium toxicity. The

100,000 g precipitate was also solubilized and examined for cadmium content. In zinc-treated embryo the cadmium content of the high molecular weight fraction was also higher than in those receiving only cadmium. This may also contribute to the zinc protection.

5. Hematopoietic System Effects

Anemia, sometimes associated with eosinophilia, has been produced by cadmium in animals. Iron and vitamin C have been reported to prevent the development of anemia (CEC 1978). Itokawa et al. (1974) administered 50 mg Cd/L (approximately 3.78 mg/kg/day, based on reported intake of 0.66 mg Cd/day and assuming a body weight of 0.175 kg) cadmium (as $CdCl_2$) to male Wistar rats (age not specified, five/group) via drinking water for 120 days. Marked fatty deposition in the bone marrow indicated possible inhibition of erythrocyte production in the pathogenesis of anemia. The number of red blood cells in cadmium-treated rats was $241 \times 10^4/mm^3$ versus $355 \times 10^4/mm^3$ in controls. The hematocrit in the experimental group was 31.7% versus 45.3% in controls and hemoglobin concentrations were 12.8 g/dL in cadmium treated rats versus control values of 17.3 g/dL. Cadmium-treated rats also had increased serum urea, phosphate and alkaline phosphatase activity and decreased serum calcium.

Decker et al. (1958) exposed groups of 34-day-old albino Sprague-Dawley rats to drinking water containing cadmium (as $CdCl_2$) at concentrations of 0, 0.1, 0.5, 2.5, 5.0, 10.0 or 50.0 mg Cd/L (approximately 0, 0.008, 0.035, 0.181, 0.361, 0.735 or 3.04 mg Cd/kg/day, based on mean final body weights of

0.413, 0.359, 0.433, 0.414, 0.415, 0.408 and 0.230 kg and mean reported water consumption of 0.030 L/day for all groups except the 50 mg/L group which consumed only 0.014 L/day). Each exposure group included eight male and eight female rats and the control group included ten rats of each sex. For the rats exposed to 0.1 to 10 mg Cd/L (0.008 to 0.735 mg Cd/kg/day) for 12 months, no adverse effects were observed in general health, growth rate or blood chemistry, and examinations for pathological changes were negative. Rats that were exposed to water containing 50.0 mg Cd/L for three months developed anemia and did not gain weight normally. The authors reported that all groups had mortality due to a respiratory infection but there was no evidence that cadmium exposure influenced the prevalence of the infection.

Prigge (1978) fed female SPF Wistar rats (age not specified) 0 to 100 mg Cd/L (as $CdCl_2$) of drinking water for 90 days but found no alteration in hemoglobin or hematocrit values. However, like other investigators, he found a decrease in serum iron concentrations. These results are presented in Table V-9.

Sutou et al. (1980b) administered various daily doses of cadmium (orally as $CdCl_2$) to male and female Sprague-Dawley rats (age not specified) for six weeks. Hematological analyses revealed an increased number of red blood cells. Hemoglobin and hematocrit were decreased. The number of white blood cells increased, mainly as a result of neutrophilia. Serum analysis indicated increased levels of glutamic-pyruvic transaminase and creatinine reflecting damage to the liver and kidneys. Increased concentrations of glucose were observed in serum of male rats. Data from the study are summarized in Tables V-10 and V-11.

Table V-9 Blood Cadmium and Serum Iron Concentrations in Cadmium Treated Rats

Cd in drinking water (mg/L)	Cd in blood (µg/100 mL)	Serum Fe (µg/100 mL)
0	-	212
25	2.64	164
50	6.36	141
100	14.71	138

Adapted from Prigge (1978).

Table V-10 Hematological Findings

Rats	Males				Nonpregnant females		
Dose (mg/kg/day)	0	0.1	1.0	10	0	1.0	10
No. of animals	14	14	14	14	2	1	8
Red blood cells ($10^4/mm^3$)	764±72[a]	726±68	755±74	836±96[b]	803±14	835	853±30[c]
White blood cells ($10^2/mm^3$)	80±16	81±16	88±20	108±17[b]	52±9.9	129	98±20.1
Hemoglobin (g/dL)	17.4±0.8	16.6±0.5[b]	17.0±0.3	17.5±0.07	16.8±5.7	16.8	14.3±1.5[c]
Hematocrit (%)	47.0±1.7	46.3±1.1	46.8±1.0	47.0±1.6	45.3±1.1	45.0	38.5±2.3[b]
Fractionation of WBC (%)							
Eosinophils					0.5±0	0.5	0.6±0.2
Neutrophils					10.8±3.2	9.0	21.1±9.5
Lymphocytes					88.0±2.8	90.0	77.7±9.7
Monocytes					0.8±0.4	0.5	0.6±0.2
Basophils					0	0	0

[a] Mean ± Standard Deviations.
[b] Significantly different from the control at P<0.01.
[c] Significantly different from the control at P<0.05.

Adapted from Sutou et al. (1980b).

Table V-11 Serum Biochemical Analysis

Parameter	Units	Male rats[a] Dose (mg/kg/day) 0	0.1	1.0	10	Nonpregnant female rats[b] Dose (mg/kg/day) 0	1.0	10
Glutamic Oxaloacetic Transaminase	K.U.	101±10[c]	102±12	99±19	100±15	114±30	97	125±10
Glutamic Pyruvic Transaminase	K.U.	32.0±6.3	33.2±7.9	31.4±4.4	31.9±6.4	26±8	25	61.4±7.8[d]
Alkaline Phosphatase	K.A.U.	9.2±2.5	11.4±4.9	10.8±4.8	12.3±5.9	7.5±1.9	4.9	7.8±2.7
Lactate Dehydrogenase	C.W.U.	165±3.4	153±54	139±41	149±38	105±13	112	149±41
Total Protein	g/dL	6.4±0.7	6.6±0.6	6.4±0.8	6.9±0.5	7.1±0.1	7.6	6.1±0.7
Albumin	g/dL	4.1±0.1	4.2±0.6	4.0±0.1[e]	3.9±0.1[d]	4.1±0.1	4.1	4.0±0.3
Globulin	g/dL	2.3±0.7	2.4±0.8	2.5±0.8	3.0±0.4[e]	3.1±0.2	3.5	2.1±0.6
Albumin/Globulin		2.0±0.8	2.3±2.0	1.8±0.7	1.3±0.4[e]	1.4±0.1	1.2	2.1±0.6
Bilirubin	mg/dL	0.28±0.04	0.31±0.05	0.27±0.05	0.30±0.04	0.25±0.07	0.3	0.28±0.05
Creatinine	mg/dL	23.1±2.6	23.6±1.2	25.1±1.5[e]	26.6±2.3[d]	24±0	27	27.9±2.0[e]
Blood Glucose	mg/dL	147±29	152±18	150±12	166±12[e]	124±23	155	130±19
Urea-Nitrogen	mg/dL	19.0±2.4	19.2±2.8	18.9±1.7	19.4±2.0	13.2±0.4	29.6	21.0±4.7

[a] Fourteen animals in each dose group.
[b] Two, one and eight animals in the dose groups, respectively.
[c] Mean ± Standard Deviation.
[d] Significantly different from the control at $P<0.01$.
[e] Significantly different from the control at $P<0.05$.

Adapted from Sutou et al. (1980b).

Anemia (reduced packed cell volume and hemoglobin), neutrophilia, lymphopenia, hypoalbuminemia, elevated α_1-, β_1- and γ-globulins, splenomegaly and cardiomegaly were observed in rabbits that ingested 14.9 mg Cd/kg/day (as $CdCl_2$ in drinking water) for 200 days (Stowe et al. 1972).

6. Cardiovascular System Effects

Kopp et al. (1978) studied the electrocardiographic, biochemical and morphological effects of chronic low level cadmium feeding on the rat heart. Eighteen female weanling Long-Evans rats were divided equally into two groups: a control group and a group administered 5 mg Cd/L (approximately 0.474 mg/kg/day, assuming 0.028 L/day and a body weight of 0.290 kg) (as the acetate) via drinking water. The average systolic blood pressures for rats fed cadmium exceeded the averages of the control animals as shown in Table V-12. A significant lengthening of the PR interval was evident in the ECG's of cadmium-fed animals, despite a more rapid heart rate. Several tests indicated that cadmium depressed the excitability of atrioventricular nodal cells and may have interfered with cell to cell conduction in the ventricle. Depressed excitability was accompanied by a 30% increase in the A-H interval of the His bundle electrogram recordings. The electrocardiologic data are summarized in Table V-13. The average cadmium concentrations in the hearts of the cadmium-fed group ranged from 50 to 900 times the concentrations found in the control group. Cadmium clearly accumulates in the heart and the data (expressed as µg Cd/g wet weight) summarized in Table V-14 suggest differences in regional uptake within the myocardium. Electron microscopy revealed

Table V-12 Average Systolic Blood Pressures for Control and Cadmium-Fed Rats

Time (months)	N	Control (average mm Hg ± SEM)	N	Test group[a] (average mm Hg ± SEM)
12	8	108±3	8	117±5
18	8	99±4	8	117±7[b]
21	8	102±5	8	119±5[b]
24	4	116±6	4	129±8

[a] Administered 5 mg Cd/L drinking water.
[b] $P<0.05$.

Adapted from Kopp et al. (1978).

Table V-13 Electrocardiology Parameters in Control and Cadmium-Treated Rats

Group	N	Rate complexes (min)	ECG		HBE		
			PR (sec)	OS (sec)	P-A (msec)	A-H (msec)	H-V (msec)
Control	4	234±23	0.056±0.002	0.024±0.002	8±1	31±2	19±1
Cadmium	4	294±23	0.073±0.004[a]	0.032±0.001[a]	9±1	40±3	22±1

[a] $P<0.05$.

Adapted from Kopp et al. (1978).

Table V-14 Tissue Cadmium Concentrations

Tissue	Cadmium concentration (μg/g±SEM) Control	Cadmium concentration (μg/g±SEM) Cadmium-fed[a]
Atria	0.007±0.007	0.363±0.21
Upper septum	0.004±0.004	0.220±0.09
Lower septum	0.002±0.002	1.742±1.61
Right ventricle	0.010±0.006	1.233±0.95
Left ventricle	0.008±0.004	1.563±1.154

[a] Administered 5 mg Cd/L of drinking water.

Adapted from Kopp et al. (1978).

degeneration within the cells of the atrioventricular nodal region and apparent increases in electron densities of the intercalated disc membranes in septal tissue. Examination of selected compounds in the heart by ^{31}P nuclear magnetic resonance spectroscopy revealed significant decreases in ATP (4.4 ± 0.8 versus 2.0 ± 0.7 μmole/g wet weight) and total adenosine nucleotide compounds (8.8 ± 0.1 versus 4.6 ± 1.0 μmole/g wet weight), with no alteration in NAD, phosphate or protein. Decreases of ADP (41%) and AMP (43%) were not significant. Thus, long-term oral exposure to low doses of cadmium is associated with depressed myocardial excitability, decreased high energy phosphate content and morphological changes.

Kopp et al. (1980) repeated the same experiment administering 5 mg Cd/L (approximately 0.286 mg/kg/day, assuming 0.028 L/day and a reported body weight of 0.480 kg) (as the acetate) via drinking water to 19 female Long-Evans rats. There were 18 similar animals as controls. No overt toxic manifestations of cadmium poisoning were observed. A summary of the physiological parameters (mean ± standard error) after 20 months of oral cadmium-exposures are provided in Table V-15. A summary of cardiac physiological indices in animals examined by ^{31}P-NMR analysis are provided in Table V-16.

More recently, Kopp et al. (1982) extended their experiments on the cardiovascular effects of cadmium at low exposure concentrations. Weanling female Long-Evans rats (a total of 520 animals) were fed (ad lib.) a rye-based low-cadmium diet and deionized water fortified with essential trace metals,

Table V-15 Summary of *In Vivo* Physiological Parameters After 20 Months of Oral Cadmium Exposure

	Control (n = 18)	5 mg Cd/L (n = 19)
Body weight, g	482±13[a]	491±19
Systolic blood pressures, mm Hg		
3 months	100±2	113±3[b]
6 months	106±2	119±3[b]
9 months	102±2	120±2[c]
12 months	102±4	122±4[b]
15 months	106±3	121±4[b]
18 months	110±4	137±3[c]
Hematocrit	(n = 10)	(n = 10)
	45±1	44±1
Electrocardiogram		
Heart rate, beats/min	260±18	253±18
P-R interval, ms	51±1	68±3[c]
Q-S interval, ms	39±2	37±2
His bundle electrogram, ms		
P-A interval	7±1	8±1
A-H interval	28±1	41±2[c]
H-V interval	16±1	20±2
Organ weights, g/kg-bw		
Heart	2.58±0.13	2.74±0.13
Liver	25.16±1.12	28.32±2.67
Kidney	2.61±0.08	2.81±0.20

[a] Mean ± standard error.

[b] Significance at $P<0.01$.

[c] Significance at $P<0.001$.

Adapted from Kopp et al. (1980).

Table V-16 Summary of Cardiac Physiological Indices and ^{31}P-NMR Analyses After 20 Months Cadmium Exposure

	Control (n = 8)	5 mg Cd/L (n = 9)
Physiological parameters		
Spontaneous heart rate, beats/min	134±5	133±6
Active tension, g	13.4±0.6	10.1±0.7[a]
P-R interval, ms	52±1	69±3[a]
^{31}P NMR (μmol/g protein)		
High-energy phosphates		
Adenosine triphosphate (ATP)	18.9±0.7	14.2±1.2[b]
Creatine phosphate (PCr)	25.2±1.7	23.5±1.8
Adenosine diphosphate (ADP)	5.7±1.2	8.2±0.7[a]
Dinucleotides	4.3±0.4	4.8±0.4
Glycerophosphorycholine	0.8±0.1	0.1±0.02[a]
Sugar phosphates	3.7±0.6	4.6±0.5
Nucleoside monophosphates	0.9±0.1	1.0±0.2
Inorganic phosphate	4.8±0.5	4.6±0.4
Total phosphate recovered, μmole/g protein	112.1±4.89	102.5±5.44
ATP + PCr	44.1±1.9	37.7±2.3[c]
ATP/ADP	3.3±0.2	1.8±0.2[a]

[a] $P<0.01$
[b] $P<0.02$
[c] $P<0.05$

Adapted from Kopp et al. (1980).

and were caged in a low-contamination environment. Nine dose levels (at least 16 rats/dose group) from 0.01 to 50.0 mg Cd/L (as the acetate) were administered via drinking water. This corresponds to doses of approximately 0.0007 to 3.45 mg Cd/kg/day, assuming drinking water consumption of 0.020 L/day and a body weight of 0.290 kg. The control population was comprised of a comparable number of rats. After 18 months at a cadmium concentration of 0.5 mg/L (about 0.03 mg/kg/day) systolic pressure was elevated by 20%; however, exposure to higher cadmium concentrations lowered systolic pressure. In a separate experiment, the effect of cadmium on cardiovascular indices and tissue metabolite concentrations was measured in rats administered 1 and 5 mg Cd/L of drinking water. Changes in blood pressure were dose-dependent and consistent with previous results. Administration of 1 mg Cd/L of drinking water had a more pronounced effect on cardiovascular indices and tissue metabolite concentrations than administration of 5 mg Cd/L. The values are consistent with those described in detail above. Although data were not presented, the authors reported that liver metabolism, as measured by changes in high-energy phosphate compounds, was only slightly altered by the doses of cadmium employed. Kopp et al. (1982) state that cytotoxic changes specific to cardiovascular tissues appear to develop in the absence of overt systemic cadmium toxicity.

Kopp et al. (1983) have continued these studies using 1 mg/L of cadmium in drinking water (about 0.062 mg Cd/kg/day, assuming water consumption of 0.030 L/day and a reported body weight of 0.483 kg). Again no overt toxicity (decreased growth rate, etc.) was observed but a persistent, mild hypertension was evident after two months. These data support the hypothesis that cadmium in environmental concentrations may contribute to essential hypertension in humans.

Schroeder and Vinton (1962) reported that long-term administration of 5 mg Cd/L (approximately 0.576 mg/kg/day, assuming 0.039 L/day and a body weight of 0.338 kg) (as $CdCl_2$) in deionized water supplemented with essential elements induced hypertension in weanling female Long-Evans rats. Systolic hypertension appeared after six to eight months. Various studies have reported that parenteral administration of cadmium will also induce hypertension in rodents (CEC 1978). However, other laboratories have been unable to confirm these findings (Porter et al. 1974, Lener and Bibr 1971). Doyle et al. (1975) reported that 5 mg Cd/L (approximately 0.315 mg/kg/day, assuming 0.021 L/day and a body weight of 0.333 kg) (as $CdCl_2$) administered to 21-day-old male and female Long-Evans rats for 320 days did not produce hypertension. Whanger (1979) summarized results of an unpublished study where 10 to 20 mg Cd/L (approximately 0 to 1.65 mg/kg/day, assuming 0.028 L/day and a body weight of 0.333 kg) (as $CdCl_2$) was administered via drinking water to OSU Brown rats for 660 days and 20 mg Cd/L was given to genetically hypertensive rats for 112 days. No statistically significant changes in blood pressure were observed.

Fingerle et al. (1982) exposed ten male and ten female Sprague-Dawley rats for 92 and 84 weeks (respectively) to concentrations of cadmium chloride in the drinking water of 5, 12.6 and 31.5 mg Cd/L. These investigations found that the weight of the kidneys, tissue cadmium residues, and severity of histological tensions in the kidneys increased in a dose-related manner; however, the blood pressure and pulse rate were not significantly affected. A review of the literature suggests that at least part of the conflicting experimental data from such studies is due to a variety of factors which have essential roles in determining the hypertensinogenic action of cadmium: age, sex, species, dietary mineral content and individual susceptibility.

Kanisawa and Schroeder (1969b) administered 5 mg Cd/L (as the acetate) via drinking water to 50 male and female Long-Evans rats from the time of weaning. Tissue examination of cadmium-exposed rats which developed hypertension revealed a typical lesion characterized by: generalized thickening of the renal arterioles and small- and medium-sized arteries, with proliferation of endothelial cells, subintimal fibroblasts and the smooth muscle cells of the media. The lumina were narrowed. These changes were confined to subintimal and medial areas of the vessels, and were similar in small arteries and arterioles. The percentage of cadmium-exposed animals developing renal vascular lesions was significantly greater than controls: glomerular capillary lesions, 88.0% versus 12.7%; arteriole lesions, 81.7% versus 1.3%; and small artery lesions, 75.7% versus 0.0%. In cadmium-exposed rats, similar lesions were discovered in the arterioles and small arteries of periadrenal fat, spleen, testis and interstitial tissue of the pancreas and salivary gland. The glomerular lesions (thickening of capsular epithelium and capillary basement membranes) were consistent with the presence of chronic benign hypertension. The systolic blood pressure of control and cadmium-exposed rats from the time of weaning are given in Table V-17. Differences between the sexes are also noted.

The relation of the renal vascular lesions to the presence or absence of hypertension (defined as systolic blood pressure > 140 mm Hg) is summarized in Table V-18. This study (Kanisawa and Schroeder 1969b) also reported significant differences in systolic blood pressure (though not to hypertensive levels) between rats raised on a low cadmium diet (0.02 µg/g wet weight) and a commercial rat chow (0.62 µg/g wet weight). Results are presented in Table V-19.

Schroeder et al. (1970) fed 42-day-old male Long-Evans BLU: (LE) strain rats low cadmium diets (0.1 µg/g wet weight) and deionized water or drinking water containing 10 mg/L cadmium (as the acetate) for 110 days. The 24 control animals had a significantly lower mean blood pressure (108 ± 3.2 mm Hg) than the 14 cadmium-exposed animals (122 ± 4.0 mm Hg). Either norepinephrine (2.5 µg) or angiotensin amide (2.5 ng) was injected intravenously to ascertain if the reactivity of blood vessels was altered. The cadmium-exposed animals had a depressed pressor response to norepinephrine (71 ± 3.4 mm Hg mean rise in blood pressure for 21 controls; 48 ± 3.7 mm Hg for nine cadmium-exposed rats) and angiotensin (24 ± 4.5 mm Hg for 11 controls; 12 ± 4.5 mm Hg for eight cadmium-exposed rats). Thus, cadmium-induced hypertension in rats may be accompanied by diminished vascular reactivity (similar to the response observed in some types of human hypertension).

Table V-17 Systolic Blood Pressure of Control and Cadmium-Fed Rats

Sex and age (months)	Controls[a]		Cadmium-fed	
	No. of rats	B.P. mm Hg	No. of rats	B.P. mm Hg
Males				
12	18	106±5.7	20	124±5.6
17	18	94±3.8	20	122±4.5
24	17	79±3.6	16	137±6.2
30	17	93±5.1	23	198±7.9
Females				
12	18	112±3.3	20	211±8.3
17	18	92±4.9	24	182±12.6
24	16	84±3.8	20	205±10.9
30	18	99±4.2	18	229±12.9

[a] Differences in the means of controls and cadmium-fed animals were significant in all pairs ($P<0.01$) except 12-month values of males.

Adapted from Kanisawa and Schroeder (1969b).

Table V-18 The Relation of Renal Vascular Lesions to Normotensive and Hypertensive Rats

Treatment	N	Glomerular Thickening		Arteriolar and arterial thickening	
		Absent	Present	Absent	Present
Cadmium					
Normotensive	4	1	3	0	4
Hypertensive	18	1	17	2	16
Control					
Normotensive	34	25	9	34	0
Hypertensive	4	1	1	1	1

Adapted from Kanisawa and Schroeder (1969b).

Table V-19 Systolic Blood Pressures of Rats Raised on Low Cadmium and Commercial Diets

Age (days)	Low cadmium diet[a]		Age (days)	Commercial diet[a]	
	No. of rats	B.P. mm Hg		No. of rats	B.P. mm Hg
89	20	85±2.2	90	29	109±3.2
120	10	87±4.4	96	10	110±3.7
150	6	81±4.2	150	10	112±6.1
328	13	84±5.8	200	8	115±4.0
387	11	82±3.4			

[a] Differences between age-matched pairs are significant ($P<0.01$) in all cases.

Adapted from Kanisawa and Schroeder (1969b).

Perry and Erlanger (1974) measured the effect of various doses of cadmium (as the acetate) administered via drinking water for as long as one year to weanling female Long-Evans rats fed a low cadmium (0.0137 mg/kg, based on random assay average) diet. Chronic exposure to cadmium was associated with a slighty increased systolic pressure (average 13 mm Hg after six months and 14 to 19 mm Hg after one year). The data are summarized in Table V-20. Rats administered 10 and 25 mg/L cadmium had smaller increases in blood pressure than those given lower doses. Rats given 50 mg/L cadmium manifested toxic signs and had significant decreases in blood pressure. Separate groups of rats were tested after one and two months of exposure. There were equivocal effects after one month, but after two months the 10 mg/L and 25 mg/L cadmium-exposed groups (16/group) had average systolic pressures of 111 and 112 mm Hg which were significantly higher than the average systolic pressure of 101 mm Hg in 32 control rats.

Perry et al. (1977a) evaluated the effect of chronic (up to 30 months) cadmium ingestion on systolic blood pressure in rats. Groups of 16 female Long-Evans rats were exposed to drinking water containing cadmium (as cadmium acetate) at concentrations of 1, 2.5, 5, 10, 25 or 50 mg Cd/L (approximately 0.075, 0.188, 0.375, 0.750, 1.667 or 5.00 mg Cd/kg/day based on assumed final body weights of 0.400 kg (for 1, 2.5, 5 and 10 mg/L groups), 0.375 kg (for 25 mg/L group) and 0.250 (for 50 mg/L group) and reported daily water consumptions of 0.030 L (for 1, 2.5, 5 and 10 mg/L groups) and 0.025 L (for 25 and 50 mg/L groups)). The control group (64 female rats) received no cadmium via drinking water. The drinking water for all groups was fortified with

Table V-20 Systolic Blood Pressure in Rats Fed Different Doses of Cadmium

N	Cd (mg/L)	Systolic pressure, 6 months (mm Hg, mean ± SD)	Systolic pressure, 12 months (mm Hg, mean ± SD)
64	0	112±15	110±14
16	1	111±20	129±16[b]
16	2.5	125±12[a]	124±16[a]
32	5	125±17[b]	127±20[a]
16	10	125±8[a]	115±15
16	25	125±16[a]	119±12
16	50	122±13	98±21[a]

[a] P<0.005.
[b] P<0.001.

Adapted from Perry and Erlanger (1974).

essential trace metals (10 mg Mn/L, 1 mg Co/L, 5 mg Cu/L, 50 mg Zn/L and 1 mg Mo/L). The animals were housed in a low-contamination environment and fed a rye-based low-cadmium diet. Systolic blood pressure was measured in triplicate at six-month intervals by the tail cuff (indirect) method. The rats were lightly anesthetized (35 mg/kg of sodium pentobarbital, ip) prior to blood pressure measurements. Groups of rats exposed to 1, 2.5, 5, 10 or 25 mg Cd/L had significantly ($P<0.01$) elevated mean systolic blood pressure (relative to controls) at one or more of the (6, 12 or 18 month) observation intervals. A significant elevation of mean systolic blood pressure was consistently observed at the 6-, 12-, 18-, 24- and 30-month observation intervals for groups exposed to 2.5 and 5 mg Cd/L.

Perry et al. (1977b) described additional studies of blood pressure responses in rats chronically exposed to drinking water containing low concentrations of cadmium. Experimental methods similar to those described in Perry et al. (1977a) were used. Groups of 20 female Long-Evans rats were exposed for 15 or 18 months to drinking water containing cadmium (as cadmium acetate) at 0.01, 0.03, 0.10, 0.25, 0.50 or 5.0 mg Cd/L (0.001, 0.003, 0.009, 0.023, 0.047, 0.467 mg Cd/kg/day, assuming a body weight of 0.290 kg and water consumption of 0.027 L/day). The drinking water was also supplemented with trace essential metals. The two control groups contained 60 and 40 rats. Systolic blood pressure was measured as previously described, with the exception that the animals were anesthetized with 25 mg/kg of sodium pentobarbital. Significant ($P<0.05$) increases in systolic blood pressure (10 to 24 mm Hg above control) were observed in animals exposed to 0.1, 0.25, 0.5

and 5 mg Cd/L for 6 to 18 months. These data are presented in Table V-21. There were no other signs of toxicity. The groups exposed to 0.01 or 0.03 mg Cd/L had average systolic blood pressures that were not significantly elevated above the controls at the end of 15 months. Perry et al. (1979) reported similar data.

As discussed above, several laboratories have been unable to confirm the findings of cadmium-induced hypertension reported by Schroeder and his colleagues (Porter et al. 1974, Lener and Bibr 1971, Doyle et al. 1975, Whanger 1979). The development of hypertension in rats depends to a large extent on the genetic background of the animal. Ohanian et al. (1978b) administered various doses of cadmium (as the acetate) via drinking water to weanling female Dahl hypertension-resistant (R) and hypertension-sensitive (S) rats on low (0.4%) or high (4%) salt diets. After 12 weeks of cadmium exposure, the S rats on low salt diets given the lowest dose of cadmium (1 mg/L) exhibited significantly higher blood pressure than the S controls. After 20 and 28 weeks, S rats fed 1 to 5 mg/L doses had significant increases in blood pressure although the high dose was not markedly changed. After 12 weeks, S rats on high salt diets and 1 or 2.5 mg/L cadmium treatment manifested significant blood pressure elevations. After 20 and 28 weeks, only S rats exposed to the 1 mg/L dose had enhanced blood pressure elevations. Cadmium or excess salt had no influence on the blood pressure of R rats. Cadmium produced cardiac hypertrophy, renal vascular changes and enhanced proteinuria in S rats on the low salt diets. These adverse effects were not detected in any R rats. Data from these experiments are summarized in Table V-22.

Table V-21 Average Systolic Pressure for Rats Exposed to "Very Low" Levels of Cadmium in Drinking Water

Cadmium exposure mg/L	No. of rats	Average systolic pressure (mmHg) at various ages (months) 6	12	15	18
First Experiment Using "Very Low" Levels of Cadmium Exposure					
Control, i.e., none	60	99±12	102±9	101±11	101±12
0.10	20	115±11[a]	116±15[a]	123±14[a]	124±15[a]
0.25	20	121±12[a]	114±12[a]	113±15[b]	120±20[a]
0.50	20	110±14[b]	113±13[a]	111±13[b]	115±17[a]
Second Experiment Using Even Lower Levels of Cadmium Exposure					
Control, i.e., none	40	106±8	103±13	99±11	
0.01	20	105±9	112±20[b]	101±10	
0.03	20	106±9	111±13[b]	102±17	
0.10	20	107±10	107±14	109±13[c]	
5.0	20	112±12[b]	119±13[a]	not done	

[a] P<0.001.
[b] P<0.05.
[c] P<0.005.

Adapted from Perry et al. (1977b).

Table V-22 Renal Vascular Changes, Proteinuria and Cadmium Levels in Kidney in Cadmium Fed Rats

Cadmium (mg/L)	Rats,[a] N	Renal vascular changes			Proteinuria (mg/100 m/L)	Cadmium in kidney (µg/g wet weight)[e]
		Absent	Mild-moderate	Marked		
Low Salt Diet (0.4%)						
0	R, 10	10	0	0	65±11	0.76±0.03
	S, 10	7	3	0	160±30	0.78±0.05
1	R, 10	9	1	0	65±11	5.71±0.53
	S, 10	3	7[b]	0	260±26[c]	10.6±0.93
2.5	R, 10	9	1	0	65±11	10.2±3.76
	S, 10	1	8[b]	1	260±26[c]	20.0±2.62
5	R, 10	8	2	0	55±15	16.4±2.31
	S, 10	1	7[b]	2	260±26[c]	38.4±5.15
10	R, 10	9	1	0	65±11	22.3±3.47
	S, 10	7	3	0	260±26[c]	82.7±14.3
High Salt Diet (4%)						
0	R, 10	9	1	0	65±11	0.90±0.14
	S, 10	0	3	7	650±116[d]	0.87±0.18
1	R, 10	10	0	0	55±15	6.85±1.18
	S, 10	0	2	8	650±116[d]	14.8±2.13
2.5	R, 10	8	2	0	65±11	13.3±3.72
	S, 10	0	2	8	650±116[d]	27.2±4.31
5	R, 10	9	1	0	65±11	20.6±5.18
	S, 10	0	2	8	650±116[d]	55.7±9.10
10	R, 10	9	1	0	65±11	30.2±3.02
	S, 10	0	1	9	650±116[d]	102.7±15.3

[a] Dahl hypertension-resistant (R) or hypertension-sensitive (S).
[b] P<0.001 compared to S control group.
[c] P<0.01 compared to low salt S group.
[d] P<0.001 compared with all low salt S groups
[e] P<0.001 all S groups compared with corresponding cadmium R rats

Adapted from Ohanian et al. (1978b).

Ohanian and Iwai (1979) confirmed and extended these findings by demonstrating (using the same protocol) that 1 mg Cd/L (as the acetate) in drinking water enhanced the rate and degree of development of salt-induced hypertension without exacerbating the hypercholesterolemia or renal vascular lesions normally observed in S rats on a high salt diet. Cadmium was found to lower circulating cholesterol levels ($P<0.01$) in both S and R lines of rats on a low salt diet after 28 weeks of treatment. Chronic excess salt feeding, regardless of cadmium intake, caused a significant rise ($P<0.01$) in plasma cholesterol in S rats as compared with the counterpart R rats. Cadmium was found to have no influence on growth, blood urea nitrogen concentration, plasma renin activity, tumor formation or survivorship in R and S rats on either low or high salt diets.

The genetic influence on cadmium-induced hypertension using Dahl rats has also been demonstrated with acute intraperitoneal routes of administration. Ohanian et al. (1978a) found that intraperitoneal administration of 2 mg Cd/kg (as the acetate), exacerbated hypertension and mortality induced by unilateral renal artery constriction (two-kidney Goldblatt procedure) in S but not R rats (12 per group). Also, renal and hepatic cadmium concentrations of S rats were significantly higher ($P<0.001$) than those of R rats.

Ohanian and Iwai (1980) reported that cadmium (2 mg/kg) administered intraperitoneally to weanling Dahl R and S rats fed a low salt (0.4%) diet followed three weeks later by another injection of cadmium (1 mg/kg ip) produced hypertension in S females but not in S males or in R rats of either sex. Furthermore, the rate and degree of salt-induced hypertension was enhanced in female S rats given cadmium at weaning (2 mg/kg ip) and at three weeks post-weaning (1 mg/kg ip). These rats were fed a high salt (4% NaCl) chow throughout the study.

Petering et al. (1979) examined blood pressure and pharmacodynamic effects of cadmium in rats. Male and female weanling Sprague-Dawley rats (36/sex) were exposed to various concentrations of cadmium (as $CdCl_2$) via drinking water. Blood pressure was elevated in male rats in a dose-dependent fashion but was not changed in female rats. The systolic blood pressures are summarized in Table V-23. Similar amounts of water were consumed by both sexes despite usual differences in body weight. Cadmium had no effect on body weight or water intake. The data for the male and female rats (32/group) are summarized in Table V-24. Female rats ingested twice the amount of water per 100 g-bw. Cadmium concentrations were higher in all organs of the females, but the increases were dose-related in both sexes. Zinc and copper were elevated in kidneys, and zinc was elevated in the liver of both sexes. Sex differences were noted in a variety of blood and serum clinical chemistry tests but cadmium contributed to none of the varying parameters. These results are consistent with studies using female Sprague-Dawley (Doyle et al. 1975) and female Wistar (Lener and Bibr 1970) rats, but contradictory to those using Long-Evans (Perry and Erlanger 1974, Perry et al. 1977a) and Dahl (Ohanian et al. 1978b) rats.

The role of cadmium as a causative agent in the induction of hypertension has been controversial. Several laboratories have reported the production of

Table V-23 Systolic Blood Pressure in Rats Treated with Different Doses of Cadmium

Cadmium concentration (mg/L)	N[b]	Systolic Blood Pressure[a]							
		29 weeks		31 weeks		36 weeks		39 weeks	
		M	F	M	F	M	F	M	F
0.0	12	118 ±8	108 ±8	125 ±3	105 ±4	117 ±3	100 ±6	121 ±5	100 ±7
4.3	8	128 ±8	102 ±6	131 ±5	99 ±4	118 ±8	104 ±4	112 ±7	97 ±7
8.6	8	136 ±6	95 ±8	137 ±7	101 ±6	127 ±4	95 ±4	132 ±4	106 ±4
17.2	8	140 ±5[c]	98 ±7	140 ±3[c]	101 ±5	132 ±3[c]	99 ±5	136 ±4[c]	91 ±6

[a] Mean systolic blood pressure in mmHg ± standard error of mean.
[b] Number of rats per sex for each exposure concentration.
[c] Significantly different from controls at $P<0.05$.

Adapted from Petering et al. (1979).

Table V-24 Means of Body Weight and Water Intake at Various Times in Male and Female Rats

	Body weight (g)		Water intake (mL)		Specific water intake (mL/100 g bw)		Statistical significance of sex effect ($P<0.01$)	
Week	Male	Female	Male	Female	Male	Female	Body weight	Specific water intake
1	42 ±5	50 ±6	--	--	--	--	N.S.	--
7	302 ±4	190 ±2	269 ±8	222 ±12	89.2 ±2.1	117.5 ±6.6	M > F	F > M
16	463 ±8	257 ±5	263 ±10	287 ±23	58.4 ±2.6	111.9 ±9.0	M > F	F > M
26	523 ±11	282 ±5	219 ±9	217 ±11	42.1 ±1.6	78.2 ±3.9	M > F	F > M
41	566 ±13	292 ±6	218 ±7	220 ±10	38.4 ±0.9	74.5 ±3	M > F	F > M

Adapted from Petering et al. (1979).

mild hypertension and several were unable to produce any change in blood pressure. Experiments by Perry and Erlanger (1982) show that diet may be a major factor in this phenomenon. Laboratories reporting cadmium induced hypertension used Schroeder's low cadmium rye-based diet composed of rye meal (60%), powdered skim milk (30%), corn oil (9%), and NaCl (1%) plus iron and vitamins. The animals also received double deionized water fortified with Mo (1 mg/L), Co (1 mg/L), Cu (5 mg/L), Mn (10 mg/L) and Zn (50 mg/L). Perry and Erlanger (1982) compared Schroeder's diet to Purina Rodent Lab Chow (Ralston Purina Co., St. Louis, MO). Female, Long-Evans rats were fed either diet in combination with the fortified water or double-distilled water (unfortified) with or without cadmium (0.1 or 1.0 mg/L). The overall effect of substituting the stock diet for the rye diet was to lessen, and even prevent, the cadmium hypertensive effect. A major reason for this was that the rats on the commercial diet exhibited a progressive, steady increase in systolic pressure of about 1 mm Hg/month, while the rats on the rye diet had a constant systolic pressure of 100 mmHg. These experiments show that diet may have a profound influence on the cadmium induced hypertension.

Perry et al. (1983) studied the effects of lead and selenium on cadmium-induced hypertension in female Long-Evans rats fed the rye-based diet over 20 months. Drinking water containing 1 mg Cd/L produced continuous hypertension which was ameliorated by giving sodium selenite (0.35 mg/L). Rats exposed to cadmium (1 mg/L) or cadmium plus lead (1 mg/L) for months four through eight remained hypertensive (for 20 months) after metal exposure was discontinued. The addition of 0.35 mg/L selenium had little effect on the hypertension in the cadmium- and lead-exposed rats. These results are shown in Table V-25.

Table V-25 Metal-Induced Changes in Average Systolic Pressure

			Average systolic pressure (mm Hg) at the indicated months after weaning								
Group	No. of Rats	Metal Exposure	4	6	8	10	12	14	16	18	20
1	14	Control (no metal)	99	98	99	102	104	105	102	99	104
2	11	4,000 mg/L Na for months 0 to 4	114[b]	102	106	--	117[c]	115	123[b]	--	125[b]
3	11	4,000 mg/L Na for months 0-4 and 1 mg/L Cd for months 0 to 20	115[b]	112[b]	118[b]	--	129[b]	131[b]	126[b]	--	133[b]
4	13	1 mg/L Cd for months 4 to 20	98	117[b]	117[b]	124[b]	123[b]	125[b]	125[b]	134[b]	132[b]
5	14	1 mg/L Cd for months 4 to 8 and 1/3 mg/L Se for months 16 to 20	98	109[c]	115[c]	116[c]	121[b]	118[c]	117[c]	107	105
6	13	1 mg/L Cd and Pb for months 4 to 20	98	118[b]	123[b]	125[b]	130[b]	127[b]	124[b]	124[b]	125[b]
7	14	1 mg/L Cd and Pb for months 4 to 8 and 1/3 mg/L Se for months 16 to 20	97	122[b]	114[b]	122[b]	119[b]	123[c]	121[b]	113[c]	117

[a] Numbers of animals and amount and timing of metal exposure (in months after weaning) are indicated for seven groups of rats. The nine columns to the right are bimonthly systolic pressure averages (mm Hg) for these groups. Eighty percent of the standard deviations were between 7 and 16 mm Hg.

[b] Significant difference from the control average (Group 1), $P<0.001$.

[c] Significant difference from the control average (Group 1), $P<0.05$.

Adapted from Perry et al. (1983).

7. Immune System Effects

Evidence indicating a cadmium-induced immuno-suppression has been accumulating. Koller (1973) administered 300 mg/L cadmium (as $CdCl_2$) in the drinking water to male New Zealand White rabbits (number and age not specified) for 70 days before inoculating them with formalized pseudorabies virus and complete Freund's adjuvant. Moderate decreases in packed cell volumes and body weight gains were noted. Mean serum-antibody titers (as the reciprocal that gave 50% reduction in serum-neutralization plaque assay) were significantly lower in cadmium exposed rabbits. Antibody titers 7 and 24 days after viral inoculation were 490 and 705 versus 2,074 and 1,667 for control subjects, respectively.

In a subsequent study, Koller et al. (1975) studied the suppressive effect of cadmium on antibody production in more detail. Swiss Webster mice (28 days old, sex not specified) were given drinking water containing either 3 or 300 mg Cd/L (approximately 0.627 or 62.7 mg/kg/day, based on a reported value of 0.0023 L/day and assuming a body weight of 0.011 kg). Three hundred ninety mice were exposed to each cadmium concentration, and 80 mice receiving deionized water were controls. The exposure period lasted ten weeks, after which all groups were supplied with deionized water. The primary immune response to injected sheep red cells was assessed (by a spleen cell plaque forming assay) during exposure to cadmium and 1, 7, 14 or 42 days after exposure ceased.

In mice which had received either dose of cadmium there was a marked reduction in spleen plaque forming cells. The number tended to increase toward control levels by 14 to 42 days after exposure in the group which had received 3 mg Cd/L but tended to stay depressed in mice which had received 300 mg Cd/L. The secondary immune response was assessed by measuring plaque-forming spleen cells in mice which were given a second ip injection of sheep red cells one week after the original injection. In both groups of animals receiving cadmium there was a depression of this secondary response as well, and by 42 days after the end of cadmium exposure the response was essentially absent.

In a similar experiment, Koller et al. (1976) administered a single dose of 0.15 mg cadmium (compound not specified), either orally or by ip injection, to 28 day-old Swiss Webster mice (80 per group). Both the primary and secondary immune responses (measured by the spleen cell plaque forming assay) were decreased by the oral cadmium dose but were increased following the ip dose. Thus, route of exposure influences the effect on the immune system.

Koller and Brauner (1977) supplied Swiss Webster CBA/J mice (28 days old, sex not specified) with drinking water containing 0, 3, 30 or 300 mg Cd/L as $CdCl_2$ (approximately 0, 0.584, 5.84 or 58.4 mg/kg/day, assuming 0.005 L/day and a body weight of 0.028 kg). After ten weeks, the ability of bone marrow-derived lymphocytes (B cells) to form rosettes was measured using an erythrocyte-antibody-complement (EAC) assay. Fewer EAC rosettes were formed by splenic B lymphocytes from mice exposed to cadmium than by B cells from control animals. The data are summarized in Table V-26. The direct effect of cadmium on B cells could account in part for suppression of the humoral immune response. The results from a similar experiment suggested that cell mediated immunity is not responsible for the suppression of humoral immunity which occurs in cadmium exposed animals (Koller and Roan 1980).

Loose et al. (1978), using *in vitro* procedures (trypan blue exclusion), demonstrated that cadmium chloride and cadmium acetate are differentially and directly cytotoxic to polymorphonucleated neutrophils, pulmonary alveolar macrophages and peritoneal macrophages. Kiremidjian-Schumacher et al. (1981a, 1981b) found that cadmium significantly interfered with the interaction between ovalbumin antigen and the surface of sensitized guinea pig spleen lymphocytes, and inhibited the production of migration inhibitory factor and the mobility of the cells. Thus, *in vitro*, cadmium appears to modify macrophage behavior through altered surface ionic configuration and interference with migration factors.

8. Pancreas Effects

The effect of cadmium on pancreatic function has attracted little interest although relatively high concentrations of cadmium accumulate in the pancreas in animals and man. Parenteral administration of cadmium will produce hyperglycemia, glucose intolerance and glucosuria. Merali and Singhal (1980) administered $CdCl_2$ in saline at doses of 0, 0.1 or 1.0 mg Cd/kg/day, orally by intubation, to newborn male Sprague-Dawley rats for 45 days (five to

Table V-26 The Effect of Cadmium on B Cells Forming Rosettes Measured with an Erythrocyte-Antibody-Complement Assay (EAC)

Dose (mg/L)	Renal concentration (μg/g)[a]	EAC (%)[b]
0	0.02	45.1
3	0.84	42.9
30	14.94	30.9[c]
300	60.50	42.7

[a] Wet weight, ten mice per group.

[b] Twenty-five mice per group; spleen cells pooled five per sample: value represents the mean of five samples.

[c] Significant, $P<0.05$.

Adapted from Koller and Brauner (1977).

six/group). Cadmium treatment caused a significant elevation of blood glucose although serum insulin levels remained within the normal range. Cadmium markedly reduced hepatic glycogen content and significantly elevated serum urea levels. Cadmium treatment also markedly elevated the activities of hepatic gluconeogenic enzymes (pyruvate carboxylase, phosphoenolypyruvate carboxykinase, fructose 1,6-diphosphatase and glucose 6-phosphatase). Some data indicating that the diabetogenic effects of cadmium may be related to an abnormal insulin secretory response of the beta cells are presented in Table V-27. Thus, chronic oral administration of cadmium to developing rats resulted in significant alterations of hepatic carbohydrate metabolism which may be associated with enhanced cyclic AMP synthesis and suppression of the insulin secretory activity of the pancreatic beta cells.

C. Other Effects

1. Carcinogenicity

Cadmium and cadmium compounds induce sarcomas at injection sites in animals when administered singly or in a repeated regimen (Haddow et al. 1964, Gunn et al. 1967).

Schroeder et al. (1965) administered 5 mg Cd/L (approximately 0.340 or 0.375 mg/kg/day for males and females, respectively, based on reported values of 0.021, 0.016 L/day and 0.308, 0.226 kg-bw for males and females respectively) (as the acetate), a dose generally considered too low for

Table V-27 Effect of Cadmium on Parameters Related to Pancreatic Function

Parameter	Control	Cd (0.1 µg/g)	Cd (1.0 µg/g)
Blood glucose (mg/100 mL)[a]	79.8	97.4[b]	108.5[b]
Hepatic glycogen (g/100 g)[a]	1.47	0.69[b]	0.44[b]
Serum urea (mg/100 mL)[a]	20.0	26.8[b]	41.6[b]
Serum insulin (µg/mL)[a]	16.35	16.23	15.04
Hepatic pyruvate carboxylase (% control)	100	141[b]	161[b]
Hepatic phosphoenolpyruvate carboxykinase (% control)	100	121[b]	130[b]
Hepatic fructose 1,6-diphosphatase (% control)	100	132[b]	187[b]
Hepatic glucose 6-phosphatase (% control)	100	119	165[b]
Glucagon-stimulated hepatic adenylate cyclase (% control)	100	114	133[b]
Insulin release from isolated islets (% control)	100	53[b]	40[b]

[a] Data represents the mean of five or six animals per group.

[b] Significantly different from control values at P<0.05.

Adapted from Merali and Singhal (1980).

carcinogenic evaluation, via drinking water, to 69 male and 58 female Long-Evans rats from weaning to death. The median ages at death were adversely affected by cadmium, with the males and females differing from controls by 156 and 140 days, respectively. Arteriolar sclerosis of the kidneys, ventricular hypertrophy and cirrhosis of the liver were prominent microscopic findings. A slight but nonsignificant increase in the number of tumors was found in cadmium-fed animals. The life-span and longevity data are summarized in Table V-28 (with number of rats corrected for mortality at less than three months of age and during an epidemic of pneumonia). The gross causes of death, including tumors, are listed in Table V-29.

Schroeder et al. (1964) also observed no excess tumors in 48 male and 39 female white Swiss CD-1 mice given 5 mg/L cadmium (as the acetate) in their drinking water for life (compared with 44 male and 60 female controls). The mean survival times for treated rats versus controls were 814 days or 957 days in males and 904 or 966 days in females, respectively.

Kanisawa and Schroeder (1969a) repeated the study in male and female weanling Long-Evans rats administered 5 mg Cd/L (approximately 0.413 mg/kg/day, assuming 0.028 L/day and 0.333 kg-bw) (as the acetate) via drinking water. Comparable results were obtained: compared to controls, there were no significant differences in the incidence of spontaneous or malignant tumors. The life-spans (days) for control and cadmium-treated rats are listed in Table V-30. The types of tumors observed in control and treated rats are summarized in Table V-31.

Table V-28 Life-Span and Longevity Data for Long-Evans Rats Fed Cadmium

	No. of rats[a]		No. dead <3	Median age at	75%	90%	Mean age of last 10%	Maximal
	Gross	Corrected	months	death (days)	dead (days)	dead (days)	surviving (days)	age (days)
Males								
Control	52	42	0	978	1,016	1,083	1,141±13.2	1,185
Cadmium	69	50	12[b]	822[b]	996	1,134	1,221±20.2	1,267 (N=4)
Females								
Control	52	44	0	945	1,036	1,156	1,245±36.0	1,400 (N=3)
Cadmium	58	46	8	805[b]	902[b]	1,018	1,146±19.4[a]	1,213 (N=1)

[a] Total number beginning experiment as weanlings, corrected for mortality at less than three months of age and during pneumonia epidemic.
[b] Significance of difference from control group $P<0.005$.

Adapted from Schroeder et al. (1965).

Table V-29 The Gross Causes of Death in Control and Cadmium-Fed Rats

	Control	Cadmium
Males		
Tumors	9	13
Metastatic	6[a]	8[a]
Pneumonia	15	17
Other infections	2	2
Hemorrhage	1	5
Neurological disease	1[a]	3[a]
Other	2	1
Unknown	6	10
No. autopsied	35	48
Females		
Tumors	15	15
Metastatic	10[a]	11[a]
Pneumonia	10	9
Other infections	1	4
Hemorrhage	3	2
Neurological disease	0[a]	7[a,b]
Other	2	4
Unknown	4	2
No. autopsied	35	36

[a] Not counted in total.
[b] Differs from control group, $P<0.001$.

Adapted from Schroeder et al. (1965).

Table V-30 Life-Spans (Days) for Cadmium-Fed Rats

	Mortality of Males			Mortality of Females		
	50%	75%	90%	50%	75%	90%
Control	872[a]	979	1,052	895	1,050	1,167
Cadmium	822	996	1,134	805	902	1,018

[a] Days.

Adapted from Kanisawa and Schroeder (1969a).

Table V-31 Type and Location of Tumors in Control and Cadmium-Fed Rats

	Control	Cadmium
No. of animals	34	47
Type of tumor		
Epithelial		
Benign	1	3
Malignant	0	2
Nonepithelial		
Benign	7	12
Malignant	2	5
Pretumorous, liver	8	8
Total lesions	18	30
Location of tumor		
Lung	0	1
Liver	1	2
Mammary gland	2	7(1)[a]
Adrenal	2	5(1)
Other	5(2)	7(5)
Total tumors	10(2)	22(7)
% with tumors	29.4	46.8

[a] Numbers in parentheses indicate number malignant.

Adapted from Kanisawa and Schroeder (1969a).

Malcom (1972) administered 0.8, 0.4 and 0.2 mg cadmium (as $CdSO_4$) in water by stomach tube to C. B. hooded rats (sex and age not specified) (25/group) once a week for two years. A control group (75 rats) was given distilled water in the same fashion. Leydig-cell tumors of the testes were seen in both control and cadmium-treated groups presumably because repeated palpation caused marked vascular damage. No other tumors were found. The results must be considered preliminary because detailed microscopic examination of prepared sections had not been completed.

Levy et al. (1975) fed eight-week-old male Swiss mice 0.44, 0.88 and 1.75 mg cadmium (as $CdSO_4$) by stomach tube once per week for 18 months (50 per treated group; 150 in the control group). Cadmium treatment did not adversely affect body weight or survival when compared to control animals. Microscopic examination of tissues revealed no significant differences between control and treated animals. Sections of the bladder and stomach revealed no abnormalities. About 80% of the liver and lung tumors were adenomas. One malignant lymphoma and one sarcoma of the myocardium was found in the control group and one localized lymphoma of the spleen was observed in the low dose group. The data for the liver and lung tumors are summarized in Table V-32.

Loser (1980) added 1, 3, 10 or 50 μg/g (approximately 0.036, 0.108, 0.360 or 2.25 mg/kg/day for males, assuming 0.0135 kg/day and a body weight of 0.375 kg for the 1, 3, 10 μg/g concentrations and a body weight of 0.300 kg for the 50 μg/g concentration and 0.047, 0.140, 0.466 or 2.33 mg/kg/day for females, assuming 0.0135 kg/day and a body weight of 0.290 kg) cadmium (as $CdCl_2$) to

Table V-32 The Tumor Incidences in Lung and Liver of Mice Fed Cadmium

Group	No. of mice from which lungs were examined	No. of mice with tumors	% with tumors	No. of mice from which livers were examined	No. of mice with tumors	% with tumors
1.75 mg Cd/kg	49	14	29	49	11	23
0.88 mg Cd/kg	50	9	18	50	18	36
0.44 mg Cd/kg	50	14	28	50	18	36
Control	149	33	22	149	50	34

Adapted from Levy et al. (1975).

the diets of four- to five-week-old SPF Wistar W.74 strain rats (50/dose/sex; 100/sex in control group) for two years. No effects were noted on food intake and survival rate at any dietary level. Growth was unchanged, except in the males receiving 50 µg/g which had a lower mean weight gain. Cadmium administered orally was not associated with an increase in the total number of tumors or in the incidence of any specific type of neoplasia, although at 50 µg/g there were adverse effects. Tumor incidences in rats fed diets containing cadmium for two years are listed in Table V-33. A summary of the tumor incidences is given in Table V-34.

Takenaka et al. (1983) have shown that lung cancer can be induced in inbred W rats by cadmium chloride aerosols. Male rats were exposed to cadmium aerosols in concentrations of 12.5, 25 and 50 $\mu g/m^3$ for 18 months. Histopathologic examinations revealed a dose dependent incidence of lung carcinomas of 15.4%, 52.6% and 71.4% (respectively). Carcinomas observed were adenocarcinomas, epidermoid, combined epidermoid, and adenocarcinomas and mucoepidermoid carcinomas. These results provide evidence for carcinogenicity of inhaled cadmium.

2. Mutagenicity

Deknudt and Gerber (1979) fed eight-week-old male C57Bl mice a low- (0.03%) or standard- (1.1%) calcium diet to which 0.06% cadmium (as $CdCl_2$) had been added. Twenty-five mice per group were maintained on this regimen for one month. The mice were sacrificed and bone marrow cells were assayed for

Table V-33 Tumor Location and Types in Rats Fed Cadmium for Two Years

Location and tumor type	Dose level (µg/g) 0	 1	Male rats 3	 10	 50	 0	 1	Female rats 3	 10	 50
No. animal examined	98	50	50	50	50	94	48	48	48	46
Pituitary										
Adenoma	22	10	16	17	7	27	10	8	11	13
Carcinoma	0	0	0	0	0	0	2	0	0	0
Thyroid										
Follicular adenoma	1	0	1	0	0	1	1	0	1	0
Interstitial cell adenoma	15	3	5	6	3	18	7	2	6	8
Interstitial cell carcinoma	1	0	0	0	0	0	0	0	0	0
Adrenals										
Phaeochromocytoma	2	0	5	2	2	1	1	1	0	2
Uterus										
Carcinoma	--	--	--	--	--	5	0	2	3	4
Leiomyosarcoma	--	--	--	--	--	0	0	0	1	0
Ovary										
Granulosa cell tumor	--	--	--	--	--	2	0	0	0	0
Cystadenoma	--	--	--	--	--	0	0	0	1	0
Mammary gland										
Adenoma	0	0	0	0	0	0	0	1	2	0
Fibroadenoma	0	0	0	0	0	2	1	4	1	0
Squamous cell carcinoma	0	0	0	0	0	0	1	0	0	0
Testes										
Interstitial cell adenoma	2	0	1	0	2	--	--	--	--	--
Lung										
Adenoma	0	1	0	0	0	0	0	0	0	0
Liver										
Hepatoma	0	1	0	0	0	0	0	0	0	0
Heart										
Endocardiac fibroma	0	1	0	0	1	0	0	0	1	0
Kidney										
Carcinoma	1	0	0	0	0	0	0	0	0	0
Thymus										
Thymoma	0	0	0	0	0	0	0	0	0	1
Pancreas										
Islet cell adenoma	2	0	0	0	0	0	0	0	0	0
Eye										
Sarcoma	0	0	0	0	0	0	0	1	0	0
Aorta										
Fibrosarcoma	0	0	0	0	0	0	0	1	0	0

continued-

Table V-33 - continued

Location and tumor type	Dose level (μg/g)									
	0	1	3	10	50	0	1	3	10	50
	Male rats					Female rats				
Brain										
Meningioma	1	3	0	0	1	0	1	0	1	0
Reticulo-endothelial-system malignant Lymphoma	0	0	0	0	0	0	0	0	2	0
Epithelial-/glandular-epithelial tissue										
Keratocanthoma	0	1	0	0	0	0	0	0	0	0
Adenoma/Cystadenoma	0	0	0	0	0	1	0	2	0	0
Carcinoma	1	0	0	1	2	4	1	1	2	1
Adenocarcinoma	0	1	1	0	0	1	1	1	1	0
Connective-tissue										
Leiomyoma	0	0	0	0	0	0	0	1	0	0
Fibroma	0	0	0	0	0	1	0	0	0	0
Sarcoma	1	2	0	0	0	0	0	0	0	0
Fibrosarcoma	0	1	0	0	1	0	1	1	1	0
Myxosarcoma	0	0	0	0	1	0	0	0	0	0
Osteosarcoma	0	0	0	0	0	0	0	0	1	0
Rhabdomysarcoma	0	0	1	0	0	0	0	0	0	0
Malignant neoplasia (not classifiable)	0	0	0	0	0	0	0	0	0	1

Adapted from Loser (1980).

Table V-34 Summary of Tumor Incidences in Rats Fed Cadmium for Two Years

	Dose level (µg/g)									
	0	1	3	10	50	0	1	3	10	50
	Male rats					Female rats				
No. of rats bearing tumors	43	21	26	24	18	54	23	17	31	25
No. of rats with benign tumors only	39	17	24	23	14	44	17	10	20	19
No. of rats with malignant tumors only	3	3	1	1	3	8	4	1	9	4
No. of rats with benign and malignant tumors	1	1	1	0	1	2	2	6	2	2
No. of rats studied histopathologically	98	50	50	50	50	94	48	48	48	46

Adapted from Loser (1980).

chromosomal aberrations. While a marked number of aberrations were noted in mice fed diets supplemented with 0.5% zinc chloride or 0.5% lead acetate, no statistically significant changes were seen in cadmium-fed mice. The data are summarized in Table V-35.

Watanabe et al. (1979) used cytogenetic analysis of mammalian oocytes to study female meiotic chromosomes for cadmium-induced germ cell mutations and chromosomal anomalies. Virgin female golden hamsters (Mesocricetus auratus) 8- to 12-weeks-old were injected with a single subcutaneous dose of 0, 1.0, 2.0 or 4.0 mg Cd/kg (as $CdCl_2$) five hours before the estimated time of ovulation--the oogenesis stages of diakinesis/metaphase I to metaphase II. Cadmium was mutagenic in this assay producing hyperhaploid and diploid oocytes as well as oocytes at the anaphase-I stage. The data are summarized in Table V-36. The ovaries of cadmium-treated (2.0 and 4.0 mg/kg) groups had severe and diffuse hemorrhages. Cadmium may have had an inhibitory effect on ovulation as well since there was a significant decrease in number of oocytes recovered per female.

DiPaolo and Casto (1979) performed quantitative studies on in vitro morphological transformation of Syrian hamster cells induced by cadmium acetate. Petri dishes were seeded with 300 cells from a secondary culture with an irradiated hamster feeder layer of 6 x 10^4 cells. Various concentrations of cadmium acetate were added 24 hours later. Dishes were fixed and stained nine days after seeding; results are summarized in Table V-37. In a series of comparative tests, cadmium and chromium were found to be the most

Table V-35 Lack of Chromosomal Aberrations in Cadmium Treated Mice

					Type and number of structural abnormalities per 100 cells			
						Chromosome		
Treatment	Calcium in diet (%)	Body weight (g)	Serum calcium (mg/100 mL)	Cells with structural aberrations	Chromatid Gaps	Gaps	Trans-locations	Dicentrics
Control	1.1	29.90	10.24	1.80	1.20	--	--	--
Control	0.03	21.80	9.45	2.00	1.80	--	--	--
Cadmium	1.1	17.65	10.26	2.20	1.80	0.20	--	--
Cadmium	0.03	14.10	8.87	1.60	1.40	--	--	0.20

Adapted from Deknudt and Gerber (1979).

Table V-36 Cytogenetic Effects of Cadmium Chloride on the Oogenesis of the Hamster *In Vivo*

	Dose of cadmium chloride (mg/kg)			
	0	1.0	2.0	4.0
Number of females examined	20 $(143)^a$	20 (164)	20 (134)	20 (95)
Number of females with chromosomally abnormal oocytes				
Hypohaploidy	2 (3)	2 (2)	4 (4)	1 (2)
Hyperhaploidy	1 $(1)^d$	1 $(1)^d$	3 $(3)^d$	4 $(4)^{b,d}$
Diploidy	0^e $(0)^e$	2^e $(2)^e$	$9^{c,e}$ $(27)^{c,e}$	$8^{c,e}$ $(16)^{c,e}$
Anaphase I	0 $(0)^d$	1 $(1)^d$	3 $(3)^d$	3 $(3)^{b,d}$
Total	3^e $(4)^e$	6^e $(6)^e$	$11^{c,e}$ $(37)^{c,e}$	$12^{c,e}$ (25)

[a] Numbers in parentheses are numbers of oocytes examined.

[b] Significant when compared with control by Fisher's exact test ($P<0.05$).

[c] Significant when compared with control by Fisher's exact test ($P<0.01$).

[d] Significant when compared with control by Chi-squared test for trend ($P<0.05$).

[e] Significant when compared with control by Chi-squared test for trend ($P<0.01$).

Adapted from Watanabe et al. (1979).

Table V-37 Transformation and Cloning Efficiency of Syrian Hamster Embryo Cells Treated with Cadmium Acetate

Cd conc. (mg/L)	No. of dishes	Total transformed colonies	Transformed colonies/dish	Ave. no. colonies/ dish	CE[a] (%)	Transformed colonies/total colonies (%)
0	11	0	0	84.4	28.1	0
0.1	8	8	1.0	67	22.3	1.49
0.5	8	14	1.75	56.5	18.8	3.1
1.0	8	9	1.12	28	9.3	4.02

[a] Determined by dividing the average number of colonies per dish by the number of cells seeded per plate multiplied by 100.

Adapted from DiPaolo and Casto (1979).

potent transforming agents relative to nickel, beryllium and arsenic. Additional experiments were done using a host-mediated in vivo - in vitro assay involving in vivo transplacental exposure of the fetuses. Pregnant Syrian golden hamsters were given 2.5 mg Cd/100 g at 11 days of gestation; embryos were excised 48 to 60 hours later. Transformation was observed in cells cloned from the third subpassage but no data were reported.

Several studies indicate that cadmium is not mutagenic. For example, cadmium did not cause significant genetic effects in Drosophila (Sorsa and Pfeifer 1973) or in germ cells of the female mouse (Suter 1975, Shimada et al. 1976). Cadmium did not increase the number of dominant lethals or induce translocations in the offspring of treated mice (Gilliavod and Leonard 1975). However, in light of those studies reporting genetic damage (e.g., Shiraishi and Yosida 1972, Shiraishi et al. 1972, Rohr and Bauchinger 1976) different methods of detecting cadmium-induced chromosome damage may be involved.

Deaven and Campbell (1980) investigated the concentration of cadmium necessary to induce chromosome damage in a widely used Chinese hamster cell line. They examined the influence of in vitro conditions on the effective threshold concentration. The threshold concentration of Cd^{2+} (as $CdCl_2$) for the induction of chromosomal aberrations in Chinese hamster ovary (CHO) cell lines cultured in F-10 medium supplemented with 15% newborn calf serum was determined to be 10^{-6}M. CHO cells grown in the presence of nontoxic levels of cadmium (2×10^{-7}M Cd) for 12 weeks became resistant to toxic levels with regard to growth rate and chromosomal aberrations. CHO cells grown in medium

Table V-38 The Relative Frequencies of Aberrant Metaphase Cell Types in CHO Cells Treated with Cadmium (1 x 10^{-6} M Cd^{2+})

Hours after Cd^{2+} addition	Mitotic index (%) (500 cells scored)	Normal (200 cells scored)	Damaged	Shattered
12	3.8	83	17	0
24	1.8	74	26	0
36	0.8	38	58	4
48	0.9	26	16	58
Control	6.6	97	3	0

Adapted from Deaven and Campbell (1980).

Table V-39 The Effect of Serum Type and Concentration on Cadmium Uptake by CHO Cells

Serum concentration (%)	Hours after Cd addition	Human serum	Newborn calf serum	Fetal calf serum
15	24	78[a]	90[a]	17[a]
15	48	74	83	16
20	24	89	94	10
20	48	80	100	23
30	24	102	82	4
30	48	105	90	12
50	24	114	74	4
50	48	118	78	8

[a] Uptake expressed as µg $Cd^{2+}/10^9$ cells.

Adapted from Deaven and Campbell (1980).

supplemented with several types of serum at concentrations commonly used for in vitro cultures (5% to 20% v/v) or found in mammalian circulatory systems (50% v/v) differed markedly in cadmium tolerance. The threshold cadmium concentration for euploid Chinese hamster cells derived from skin, lung and kidney tissues was determined to be 2 x 10^{-5}M. Cadmium did not induce elevated chromatid exchange levels. The relative frequencies of aberrant metaphase cell types following treatment of CHO cells with 10^{-6}M cadmium are shown in Table V-38. The effects of serum type and concentration on cadmium uptake (expressed as μg Cd/10^9 cells) by CHO cells are shown in Table V-39. The authors suggest that the results demonstrate the necessity for standardized protocols for cytogenetic investigations of cadmium toxicity and may help to explain the discrepancies between studies of chromosome damage in patients with high cadmium blood levels.

3. Reproductive and Teratogenic Effects

Parenteral, especially intravenous, administration of cadmium can produce profound teratogenic effects (Gale and Layton, 1980). Sutou et al. (1980a) administered 0, 0.1, 1.0, and 10.0 mg Cd/kg/day (as $CdCl_2$) orally to male (14/group) and female (14/group) adult Sprague-Dawley rats for six weeks. Males and females within each group were mated six days a week for three weeks, changing partners every week, if necessary. Cadmium was also administered during the three-week mating period. Pregnant females were given cadmium during the gestation period and sacrificed on the 20th day of gestation for teratogenicity tests. Two virgin females per male per week were mated for six weeks. Pregnant females were sacrificed on the 13th day of gestation for dominant lethal tests. The number of total implants and live fetuses decreased significantly in the high dose group and the number of resorbed fetuses was markedly increased. Five fertility indices (copulating ability and impregnating ability of males and copulated ratio, pregnant ratio and pregnancy efficiency of females) were measured and generally found not to be significantly different from controls. The effect of cadmium on some fertility factors are summarized in Table V-40. Fetuses from the high dose group showed decreased body weight, body length and tail length and increased placental weight as indicated in Table V-41. Examination of the viscera of about one-third of the fetuses revealed no specific anomalies attributable to cadmium toxicity, although hemorrhages in various areas and dilation of the renal pelvis were noted. Skeletal examinations of the remaining two-thirds of the fetuses revealed delayed ossification of the sternebrae and caudal vertebrae. Dominant lethal tests measured the number of impregnated females and the average number of corpora lutea, total implantations, preimplantation losses, live fetuses and early, late and total deaths per female. There was no significant difference from controls. The authors suggest anemia and hormonal imbalance may be the cause of the impaired fertility and fetotoxicity.

Ahokas et al. (1980) studied cadmium-induced fetal growth retardation. Various levels of cadmium as $CdCl_2$ were given via drinking water to pregnant Sprague-Dawley rats (ten/group) during gestation. Maternal daily food and water consumption, total weight gain, maternal weight and feed efficiency all

Table V-40 The Effect of Cadmium on Several Fertility Factors

Dose (mg/kg/day)	No. of animals	Copulating	Pregnant	Corpora lutea	Total implants	Live fetuses	Macerated	Resorbed
0	14	14	11	15.2±2.0[a]	14.7±2.0	14.2±2.0	0	0.55
0.1	13	13	10	14.2±2.0	13.9±1.7	13.9±1.7	0	0.70
1.0	13	12	12	15.5±1.8	13.6±1.8	13.1±2.3	0	0.50
10	13	5	5	13.6±1.5	10.6±3.1[b]	7.2±2.4[b]	0.8	2.6[c]

[a] Mean ± SD.
[b] Significantly different from the control at $P<0.01$.
[c] Significantly different from the control at $P<0.05$.

Adapted from Sutou et al. (1980a).

Table V-41 The Effect of Cadmium Treatment on Fetal Size and Placenta Weight

Sex of fetuses	Males				Females			
Dose (mg/kg/day)	0	0.1	1.0	10	0	0.1	1.0	10
No. of fetuses	71	73	73	15	85	59	84	21
Body weight (g)	3.63±0.10[a]	3.58±0.23	3.52±0.27	2.41±0.29[b]	3.48±0.16	3.40±0.25	3.37±0.23	2.32±0.23[b]
Body length (mm)	39.1±0.4	39.2±0.9	39.0±1.1	35.2±1.0[b]	38.5±0.5	39.4±3.4	38.2±0.8	34.3±1.2[b]
Tail length (mm)	13.8±0.3	13.7±0.3	14.0±0.5	12.3±1.1[c]	14.1±0.3	14.0±0.5	14.3±0.3	12.5±0.9[c]
Placenta (mg)	502±25	524±60	530±49	548±46[c]	479±30	501±78	500±57	554±73[c]

[a] Mean ± Standard Deviation.
[b] Significantly different from the control at $P<0.01$.
[c] Significantly different from the control at $P<0.05$.

Adapted from Sutou et al. (1980a).

decreased with increasing cadmium consumption. Fetal levels of cadmium were low (0.038 to 0.095 μg/g fetus) and did not increase with increasing cadmium consumption while placental cadmium increased more than ten-fold (to 1.124 μg Cd/g wet weight in those fed the high dose). Fetal zinc levels decreased in cadmium-fed dams and zinc supplementation (5 μg/mL drinking water) increased fetal zinc levels though not to control levels. Term fetal weight in the high dose group was significantly less than that of controls. Due to reduced litter size, total litter weight gradually decreased with increasing cadmium concentration. Results of the study are summarized in Table V-42. Fetal growth retardation appeared to result from decreased cell division (DNA) and cell growth (protein/DNA ratio). When dams in the high dose group were pair fed, the average amount of food consumed daily, maternal weight gain, fetal weight, and DNA and protein/DNA ratio were increased though not to control levels. Dietary zinc supplementation of cadmium-fed dams increased maternal food consumption, fetal weight, and DNA and protein/DNA ratios to control levels. Some of the data are summarized in Table V-43. The authors suggested that cadmium-induced fetal growth retardation is an indirect effect resulting from reduced maternal food consumption and metabolism and zinc deficiency. Cadmium-induced placental necrosis may also play a role in the adverse consequences seen in the reproductive processes.

Christley and Webster (1983) injected pregnant C57BL/6J mice with a single dose of cadmium in a teratogenic (2.4 mg Cd/kg), an intermediate (40 μg/kg) or a trace (0.66 μg/kg) dose of $CdCl_2$ (^{109}Cd-20 μCi) on day nine of gestation. The amount of radiolabel was measured at 1, 12, 24 and 240 hours

Table V-42 The Effect of Cadmium Exposure on Litter Parameters and Placental Weight

	Drinking water Cd concentration (mg/L)				Pair-fed control	100 mg Cd and 5 mg Zn/L
	0	1	10	100		
Number of litters	10	8	8	7	8	10
Litter size	13.3±0.5[a]	10.8±0.6	11.3±0.6	11.9±0.7	10.8±0.8	10.6±0.7
Total litter weight (g)	69.1±3.1	61.5±2.8	59.4±4.3	44.0±4.5[b]	46.9±2.7[b]	52.5±4.0[b]
Fetal weight (g)	5.19±0.07	5.52±0.07	5.22±0.15	3.79±0.27[b]	4.47±0.28	4.97±0.19
Placental weight (g)	0.66±0.04	0.76±0.04	0.70±0.04	0.66±0.02	0.58±0.03	0.78±0.04

[a] Values reported are mean ± standard deviation.
[b] Significantly different from control ($P<0.05$).

Adapted from Ahokas et al. (1980).

Table V-43 The Effect of Cadmium on Fetal DNA and Protein

	Drinking water Cd concentration (mg/L)				Pair-fed control	100 mg Cd and 5 mg Zn/L
	0	1	10	100		
Concentration (mg/g)	4.07±0.13[a]	4.16±0.18	4.38±0.16	4.29±0.09	4.13±0.07	4.60±0.19
DNA						
Total (mg)	21.23±0.73	23.21±1.03	23.09±1.12	16.12±0.87[b]	18.43±0.99	22.14±0.75
Concentration (mg/g)	106.95±3.20	92.61±4.81	88.70±3.98[b]	100.21±4.63	103.52±2.20	109.67±3.28
Protein						
Total (mg)	558.5±19.7	516.7±25.4	470.0±32.8	378.8±32.5[b]	463.6±29.8	544.4±24.4
Protein/DNA ratio	26.56±1.25	23.27±1.43	20.30±0.72[b]	23.41±1.22	25.12±0.64	24.14±1.01

[a] Values reported are mean ± standard deviation.
[b] Significantly different from control value ($P<0.05$).

Adapted from Ahokas et al. (1980).

after administration. For all doses, Cd rapidly entered the embryo with high levels at one hour, declined during the next 11 hour, rose again at 24 hour, and remained high. Autoradiographic studies showed that the teratogenic dose of cadmium entered all tissues of the embryos but was particularly localized in cells in the neural tube, limb buds and gut. By 12 hours cell damage was observed in the embryo but the damaged cells were not necessarily the cells with the most radioactivity.

Cadmium administered by parenteral routes may induce acute testicular necrosis. Species with intra-abdominal testes are usually resistant to this effect, but those with scrotal testes are generally susceptible (CEC 1978). Parizek (1957) administered subcutaneous injections of 0.02 mmol cadmium (as the chloride or lactate)/per kg to adult male Wistar rats and observed macroscopic changes in the testicles within a few hours. The organs first became swollen and dark red or purple. The weight of the testicles then decreased rapidly and the organs became small, hard and yellowish. The weight of the seminal vesicles and the prostate decreased as a result of decreased endocrine activity of the testicles. Histologically, a capillary stasis and edema of the interstitium followed by extensive hemorrhages were observed. Regressive changes of the seminiferous epithelium were seen shortly after injection and progressed to total necrosis within 24 to 48 hours. Dependent on dose, after acute necrosis a revascularization of the testicles, regeneration of Leydig cells, and increased endocrine activity may occur after one month. While several studies have confirmed the acute toxic insult of cadmium to the testes, little corroboration exists in chronic exposure tests.

Ribelin (1963) reported histological changes in the testicles of rats as a result of long-term (4.6 to 17 weeks) administration of 500 to 1,270 µg/g cadmium via food. The changes reported were different from those developed after a single injection but were not different from those produced by several other toxic substances tested by Ribelin. It is impossible to judge the frequency of the changes since no data are given concerning the number of animals, frequency of testicular alterations or appearance of toxic reactions in other organs (Friberg et al. 1974).

Kotsonis and Klaassen (1978) detected no testicular effects (histopathological or functional) following chronic oral exposure. Male Sprague-Dawley rats (50- to 70-days-old) received 10, 30, and 100 mg Cd/L (as $CdCl_2$) via drinking water for 24 weeks. Testicular function was assessed via a mating technique in which each male was mated with one untreated virgin female the week prior to sacrifice of the male. Fourteen days after the mating period, a laparotomy was performed on each female rat, the uterine horns were exteriorized, and the number of fetuses was recorded. The numbers of females producing offspring and the number of fetuses per pregnant rat were not significantly different when females mated with control rats were compared to females mated with treated rats.

Wong and Klaassen (1980b) administered 1 mg Cd/kg labeled with $^{109}CdCl_2$ (30 µCi/mg specific activity) via the femoral vein to male Sprague-Dawley rats of 4-, 21-, and 70-days-of-age. Two hours after administration, the concentrations of cadmium in the testes of newborn and weanling rats were found to be 5- and 2.5-times higher, respectively, than that in the adults. The percentage of the dose in the testes was lower in the four-day-old rats than in the adults during the first two days after injection because the testes in adults constitute a much higher percentage of body weight than in younger animals. During the first two days after injection, the testes increased in size in the adults, but the size decreased dramatically thereafter. The change in testicular size is attributed to the toxic effects of cadmium on the testes. In the immature rat the testicular weight increased with time. Thus, the blood-testes barrier for cadmium appears to be partly developed in rats by 21-days-of-age.

Hastings et al. (1978) fed two male and four female adult Sprague-Dawley rats 17.2 mg Cd/L via drinking water for 90 days. Breeding trials between control males and females and cadmium-exposed males and females were conducted with continuous cadmium exposure through gestation. The effects of dietary cadmium on the neonates are summarized in Table V-44. Only pup birth weight and total body iron levels were altered by the cadmium exposure. Wahmann wheel running activity was monitored for five weeks beginning at 35 days of age. Rats prenatally exposed to cadmium showed a significant reduction in spontaneous locomotor activity but were normal in growth, food and water consumption. No significant behavioral differences were noted between the two groups in the number of days to criterion in the acquisition or reversal or in mean response latencies of a cued spatial discrimination task.

Grady et al. (1978) reported adult pituitary-adrenal alterations in mice exposed to cadmium in utero and neonatally. Pregnant 129/SvSl mice were

Table V-44 The Effect of Cadmium (17.2 mg/L) on Neonatal Parameters

Neonatal parameter	Group control mean ± S.E.M.	Cadmium treated mean ± S.E.M.
No. of pups/litter	11	12
Pup birth weights (g)	6.8±0.1	6.0±0.2[a]
Weight at weaning (g)	58.0±0.6	59.0±0.6
Whole pup body:		
Zinc (μg/g)	119.0±5.0	125.0±5.0
Copper (μg/g)	11.0±0.8	12.0±0.9
Iron (μg/g)	327.0±24.0	207.0±16.0[a]
Cadmium (μg/100 g)	16.0±2.2	17.0±2.4

[a] $P<0.01$.

Adapted from Hastings et al. (1978).

orally gavaged with 2 mg Cd (as the chloride)/kg on days 15, 17 and 19 of gestation and on alternate post-partum days until post-partum day 20 (13 treatments). Offspring were tested for pituitary-adrenal axis parameters at 277- and 460- to 480-days-of-age. Young cadmium-exposed females showed only suggestive differences in adrenal steroidogenesis. However, at 460 to 480 days of age marked alterations in endocrine function were found in mice of both sexes. Enhanced adrenal production of corticosterone and a concomitant elevation in resting plasma corticosterone levels were found in females. Increased adrenal weight was found in males, but other adrenal functions were unchanged. Significant elevations in liver metabolism of corticosterone were seen when measured as total and A-ring reduction. These perturbations were explained by the authors on the basis of increased activities or amounts of hepatic steroid reductases, increased availability of essential cofactors, such as NADPH or glucose-6-phosphate dehydrogenase, or altered gonadal hormone (estradiol or testosterone) influence on hepatic metabolism. Results of the study are summarized in Table V-45.

D. Summary

Cadmium has no known beneficial effects, and it is toxic to animals and humans. Oral LD_{50} values in the rat are about 100 to 500 mg/kg for soluble cadmium salts and are about 1,000 to 5,000 mg/kg for insoluble salts. Parenteral administration of 1 to 10 mg/kg causes damage to many tissues, including liver, renal cortex and spinal ganglia.

Table V-45 The Effect of Cadmium on the Pituitary-Adrenal Axis of Male and Female Mice

Parameter	277 day old				460-480 day old			
	Male		Female		Male		Female	
	Control	Cadmium	Control	Cadmium	Control	Cadmium	Control	Cadmium
Number of animals	5	5	5	5	5	9	4	7
Body weight (g)	26.5±0.5	23.1±1.2	22.9±0.2	26.0±0.6[a]	27.4±0.8	29.6±0.6	27.0±1.8	22.4±0.6[a]
Liver weight (g)	1.09±0.03	1.13±0.04	0.80±0.04	1.06±0.11[b]	1.38±0.06	1.36±0.03	1.12±0.04	1.03±0.03
Liver reduction of corticosterone[c]								
Total/200 mg	25.0±1.0	23.2±0.6	16.8±0.8	15.8±1.2	27.0±1.7	32.4±1.2[a]	20.0±0.7	19.4±0.8
Total/liver	137.6±9.0	132.0±6.7	67.6±4.4	84.5±10.0	187.3±15.8	221.1+10.1[b]	111.7±6.9	100.0±4.1
A-ring/200 mg	24.1±1.9	23.1±0.8	14.0±1.5	15.4±1.6	22.5±2.2	29.1+1.7[b]	10.6±0.7	12.8±1.7
A-ring/liver	131.4±14.0	131.0±5.7	56.9±8.0	80.3±6.6	156.6±17.5	198.3±12.5[b]	59.5±4.9	66.9±9.8
Side-chain/200 mg	10.4±1.1	11.8±1.0	9.9±0.7	10.1±1.4	8.3±0.6	10.8±1.0	9.6±1.2	7.4±0.8
Side-chain/liver	57.0±6.2	66.8±5.8	39.4±1.6	53.7±7.7	57.7±5.6	73.7±7.3	53.5±7.3	37.8±4.4
Adrenal weight (mg)	3.5±0.2	4.0±0.2	4.6±0.2	5.3±0.3	3.6±0.3	4.4±0.3[b]	4.3±0.2	4.6±0.2
Adrenal production of corticosterone in vitro[d]	30.5±4.4	34.2±1.0	80.0±11.0	61.9±3.0	17.2±2.6	23.3±2.6	35.2±5.0	71.9±5.2[a]
Plasma corticosterone[e]	4.1±0.7	5.0±1.7	12.3±1.7	8.4±1.7	4.9±0.5	4.1±0.3	4.7±0.5	6.7±0.3[a]

[a] $P<0.01$.
[b] $P<0.05$.
[c] µg corticosterone reduced/30 minutes.
[d] µg corticosterone/100 mg adrenal.
[e] µg corticosterone/dL.

Adapted from Grady et al. (1978).

The effects of chronic oral exposure to lower levels of cadmium have received considerable attention. One organ which is clearly injured by cadmium is the kidney. Rats administered 30 or 100 mg Cd/L cadmium in their water (about 2.2 or 6.4 mg Cd/kg/day) for six weeks or longer developed proteinuria, while rats administered 10 mg/L (about 0.8 mg Cd/kg/day) did not develop significant proteinuria. Rats administered drinking water containing 25 to 100 mg Cd/L (about 3 to 12 mg Cd/kg/day) for 90 days showed nearly a two-fold increase in urinary protein concentration. Proteinuria and aminoaciduria were observed in rats receiving 1 mg Cd/kg/day (given ip, five days per week for 3 months). The renal cadmium content of these animals was 230 µg/g tissue (compared with 0.2 µg/g in control animals). Rats administered drinking water containing 10 to 300 mg/L cadmium (about 0.5 to 14 mg Cd/kg/day) for 6 to 40 weeks showed histological signs of renal damage, including an increase in lysosomes and swelling of mitochondria. In rabbits administered 14.9 mg Cd/kg/day for 200 days, cortical necrosis and fibrosis were observed primarily in the proximal tubule. Rats administered 0.1 to 5 mg Cd/kg/day exhibited renal vascular constriction and scarring of peritubular capillaries. This may be related to cadmium induced hypertension (see below).

The liver is also affected by cadmium ingestion. Rabbits administered 160 mg Cd/L in their water (about 15 mg Cd/kg/day) for 200 days showed loss of hepatic glycogen, inflammation and deposition of collagen, biliary hyperplasia and proliferation of the smooth endoplasmic reticulum. Liver cadmium levels in these animals were 188 µg Cd/g tissue. There was no change in a number of standard tests of liver function (serum glutamic oxaloacetic transaminase, alkaline phosphatase, clotting time, etc.), showing that such tests may not reveal sub-clinical liver injury. Rats receiving 17 mg Cd/L in water (about 1.6 mg Cd/kg/day) for 280 days showed similar changes (glycogen loss, altered mitochondrial morphology, SER proliferation), and these effects were more pronounced in rats receiving a diet deficient in zinc and copper.

Another prominent consequence of chronic cadmium ingestion is osteomalacia. Rats receiving 100 µg Cd/g chow in the diet (about 5 mg Cd/kg/day) for 500 days showed loss of bone calcium, decreased plasma calcium and increased urinary calcium. Deleterious effects of cadmium on the skeleton are increased by diets low in calcium or vitamin D, and it has been suggested that effects on bone may be secondary to altered calcium or vitamin D metabolism.

Bone marrow is also injured by cadmium, resulting in anemia. Rats administered 50 mg Cd/L (about 3.8 mg Cd/kg/day) in water for 120 days showed fatty marrow, decreased red blood cell count (from 355 to 241 x 10^4 cells/mm^3), decreased hemoglobin (from 17.3 to 12.8 g/dL), and decreased hematocrit (from 45% to 32%).

Cells of the immune system are affected by cadmium. In rabbits receiving 300 mg Cd/L in their water (about 20 mg Cd/kg/day) for 70 days, the titer of immune serum produced in response to a viral antigen was decreased by two- to four-fold. Mice receiving 3 to 300 mg Cd/L in their water (about 0.6 to 60 mg Cd/kg/day) for 70 days showed decreased immunologic activity of β-cells.

Renal cadmium concentrations in these animals ranged from 0.84 to 60.5 µg Cd/g tissue (versus 0.02 µg/g in control animals). Mice receiving 3 mg/L (0.63 mg Cd/kg/day) for 10 weeks showed decreased production of both IgM and IgG. After exposure to cadmium was discontinued, IgM production returned within 14 days, but IgG production remained repressed for 42 days.

The pancreas accumulates significant quantities of cadmium, but effects of cadmium on pancreatic function are not well studied. Rats administered 0.1 or 1 mg Cd/kg/day (orally) for 45 days showed elevated blood glucose (from 80 to 108 mg/dL), decreased liver glycogen (from 1.5 to 0.4 g/100 g), but did not show a significant change in serum insulin levels. Nevertheless, the insulin secretory response of isolated islets was reduced by 50% to 60%. One factor contributing to the hyperglycemia appeared to be increased gluconeogenesis by liver, since the activities of four key gluconeogenic enzymes were increased by 20% to 60%.

Chronic cadmium ingestion has been implicated as a cause of hypertension, but there is considerable controversy regarding this issue. Several studies have found that rats receiving drinking water containing 5 mg Cd/L (about 0.5 mg Cd/kg/day) developed significant hypertension (usually an increase of 10 to 20 mm Hg systolic blood pressure over control animals) after periods of time from 3 to 18 months. Conversely, several other studies in which rats received similar amounts of cadmium (5 to 20 mg/L in water) for periods from 11 to 23 months did not reveal significant hypertension. Several studies have shown differences between animal strains and sex with regard to sensitivity to cadmium-induced hypertension, and this may underlie some of the variation in results. However, an even more significant variable may be the diet supplied. The effects of cadmium in water on blood pressure are most clear when the diet is specially formulated to be low in cadmium (0.02 µg/g versus 0.62 µg/g in standard chow). Rats raised on such a low cadmium diet have lower blood pressure than rats raised on commercial chow (85 versus 109 mm Hg), and blood pressure tends to increase with age in rats receiving commercial chow (from 109 to 115 mm Hg) while it remains nearly constant in rats on a low cadmium diet. Thus, cadmium levels as low as 0.1 mg/L in drinking water may produce a measurable increase in systolic blood pressure in rats on a low cadmium diet, but do not produce significant effects in animals receiving a normal diet.

Several studies have been performed to determine the carcinogenic potential of orally ingested cadmium, and all have yielded negative results. In one case, rats receiving 5 mg Cd/L (about 0.3 to 0.4 mg Cd/kg/day) in water for life showed decreased life span, sclerosis of renal arterioles, ventricular hypertophy, and liver cirrhosis, but no significant increase in tumor frequency. In another study, rats receiving up to about 2.3 mg Cd/kg/day in the diet for two years showed no change in survival rate and, as above, no increase in tumor rate. Likewise, rats administered up to 0.8 mg cadmium (orally, as $CdSO_4$, once per week for 2 years) did not show a significant increase in tumor frequency. Inhalation of cadmium aerosols (12 to 50 $\mu g/m^3$) for 18 months did result in increases (15% to 71%) in the number of lung carcinomas in rats.

Cadmium exposure has been found to result in chromosomal damage in several test systems. For example, subcutaneous injection of 1 to 4 mg Cd/kg (as $CdCl_2$) five hours before ovulation in female hamsters resulted in a six- to nine-fold increase in the number of chromosomal abnormalities found in oocytes. Likewise, several lines of cultured hamster cells exposed to cadmium *in vitro* at concentrations from 0.11 to 2.24 mg Cd/L (10^{-6} M to 2×10^{-5} M) showed chromosomal aberrations and increased transformation frequency. On the other hand, several studies in mice and *Drosophila* have found no evidence of cadmium-induced genetic damage. Such discrepancies may result from different methods of detecting chromosomal abnormalities.

Cadmium exposure has effects on reproduction in both male and female animals. Male rats receiving cadmium in food (500 to 1,270 µg/g, long term), or by injection (1 mg Cd/kg) showed a number of signs of testicular damage, although male rats receiving 10 to 100 mg Cd/L in water for 24 weeks did not show reduced fertility. Female rats receiving cadmium in a variety of regimens before and during gestation produced litters of decreased size and weight. Experiments with $^{109}CdCl_2$ given on day nine of gestation showed that the label rapidly enters the fetus (by one hour), and remained present for up to ten days. Live pups from cadmium-treated mothers showed delayed ossification, decreased motor activity and altered renal steroidogenic activity. Growth rate, food consumption and a test of conditioned response showed no difference from control.

VI. HEALTH EFFECTS IN HUMANS

A. Acute Toxicity

In humans, acute cadmium intoxication is usually the result of ingestion of food or beverages contaminated by storage in cadmium-plated containers. Accidental ingestion of silver polish containing cadmium carbonate has also caused intoxications. The first symptoms occurring after acute ingestion of cadmium are severe nausea, vomiting, diarrhea, muscular cramps and salivation (Arena 1963). Sensory disturbances, liver injury and convulsions have been observed in severe intoxications. In fatal intoxications, these symptoms are followed either by shock due to dehydration and death within 24 hours or by acute renal failure, cardiopulmonary depression and death within 7 to 14 days (CEC 1978). The prohibition by health authorities of cadmium-plated containers has reduced the incidence of this form of acute poisoning (CEC 1978). Cadmium fumes and dusts are highly toxic; they may produce metal fume fever or a more severe intoxication involving the lungs (pulmonary inflammation, edema, pleurisy, emphysema). There are no reports of systemic toxicity following topical exposure.

Treatment of acute cadmium salt ingestion generally involves induction of emesis followed by gastric lavage, a saline cathartic and demulcents. Atropine, opiates and fluid therapy are sometimes recommended as adjunct treatments. Calcium-sodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) has been used to treat some human intoxications. Once cadmium becomes bound to metallothionein in liver and other organs, the efficiency of some of the commonly employed chelating agents in removing cadmium diminishes (Cherian 1980). BAL (2, 3-dimercaptopropanol) has been suggested as a potential agent for use in chelation therapy, however, the BAL-cadmium complex, like other cadmium-thiol complexes, has a nephrotoxic action and extreme caution would be warranted.

Truffert reported that poisoning has resulted from the accidental consumption of coffee and wine containing 800 and 126 mg/L cadmium, respectively (CEC 1978). Punch containing 67 mg/L cadmium has caused sickness (Frant and Kleeman 1941). Assuming 200 to 500 mL were consumed, this represents a cadmium intake of 13 to 35 mg (CEC 1978). Nordberg et al. reported acute poisonings in a group of Swedish school children who consumed fruit drinks from a distributing machine with a cadmium-plated reservoir; the Swedish National Food Administration found that the concentration of cadmium in the water used for dilution ranged from 0.5 to 16 mg/L (Carstensen and Poulsen 1973).

The threshold for an emetic effect (nausea and vomiting) in humans was estimated to be a dose of 3 mg Cd (0.043 mg/kg for 70-kg adult) (CEC 1978). Lauwerys (1979) also estimated the no-effect level for a single oral dose to be 3 mg Cd. Friberg et al. (1979) reported that ingestion of water containing 15 mg Cd/L could induce the emetic response in humans. Assuming that eight ounces of water were ingested, the dose for the emetic effect was calculated to be 3.6 mg (15 mg Cd/L x 0.240 L = 3.6 mg). Thus, the dose-estimate based on the 15 mg/L concentration reported by Friberg et al. (1979) is also consistent with the 3 mg threshold dose for the emetic effect reported by CEC (1978) and the no-effect level reported by Lauwerys (1979). A dose scale of acute oral toxicity of cadmium to man has been elaborated in Table VI-1.

The lethal human dose of cadmium oxide fumes has been estimated to be 1,500 to 2,900 min mg/m^3 (although much lower levels can incapacitate) (Barrett and Card 1947, AIHA 1962). Extrapolation from this time-dependent lethality value yields concentrations of 3.1 to 6.0 mg/m^3 for an 8-hour exposure or 150 to 290 mg/m^3 for a ten minute exposure. Exposures of 0.5 mg/m^3 in workroom air have been linked to mild cases of pneumonitis (Wilcox 1973).

B. Chronic Toxicity

Cadmium is biologically active in experimental animals at concentrations to which the average American is exposed (e.g., see Kopp et al. 1982). However, aside from those studies linking cadmium ingestion to Itai-Itai disease in Japan, there is no substantial or unequivocal evidence implicating chronic ingestion of cadmium in nonoccupational settings with any human ailment or disease. This section describes the chronic toxicities induced by cadmium primarily from occupational exposures.

1. Effect on the Kidneys

Cadmium-induced kidney lesions have been observed in workers exposed to airborne cadmium dusts and fumes and in subjects who ingested contaminated

Table VI-1 Dose Scale of Acute Oral Cadmium Toxicities in Humans

Dose	Effects
<3 mg	No effect level for single oral dose
3-90 mg	Emetic threshold Non-fatal incidents
15 mg	Experimentally induced vomiting
10-326 mg	Severe toxic symptoms without fatality
350-3,500 mg	Estimated lethal doses
1,530-8,900 mg	Reported lethal doses

Adapted from CEC (1978).

food and water (mainly older Japanese women with Itai-Itai disease), especially rice grown in soils irrigated with polluted water (CEC 1978). In exposed workers, kidney lesions usually precede lung damage (Lauwerys et al. 1974, Adams et al. 1969, Piscator 1962a).

The initial cadmium-induced kidney lesion, preceding other functional damage, involves the proximal tubules. The lesion gives rise to a "tubular" type proteinuria (described below) with a predominance of low molecular weight proteins like β_2- microglobulin, lysozyme, ribonuclease, retinol binding protein and immunoglobulin chains (CEC 1978). A low molecular weight (approximately 20,000) albumin (minialbumin) and a "glomerular" pattern of increased high molecular weight protein clearance may accompany the tubular lesion (Kench et al. 1965, Bernard et al. 1976, Roels et al. 1974). The proteinuria may remain after the individual has been removed from exposure (Piscator 1962a,b). Cadmium-induced proteinuria may be associated with glucosuria, aminoaciduria, decreased concentrating capacity of the kidney, impaired acid excretion, increased calcium and phosphorus excretion and altered uric acid disposition (Adams et al. 1969, Kazantzis et al. 1963, Piscator 1966, Smith et al. 1961, Bernard et al. 1976). After renal damage develops, cadmium concentrations in the kidney decrease presumably due to increased urinary excretion. However, no direct experimental data in humans has been reported.

As indicated earlier the renal cortex is an important cadmium storage site. The concentration of cadmium in the kidney increases with the intensity and duration of exposure over extended periods.

Nomiyama et al. (1973) examined urine samples from seven Japanese female patients diagnosed with Itai-Itai disease. Proteins with molecular weights between 12,000 and 45,000 were detected in the urine, indicating impaired protein resorption in the proximal tubules. The urine sample of one patient was more carefully analyzed for molecular size distribution of proteins by column gel filtration; the major low-molecular weight proteins were found to be of 12, 21, 45 and 54 x 10^3 molecular weight. The results of analyses of these proteins by counterimmunoelectrophoresis are presented in Table VI-2. The range of values from the medical history and renal function tests for the patients are presented in Table VI-3. The authors also commented that treatment with large doses of vitamin D probably aggravated the renal tubular dysfunction.

Kjellstrom et al. (1977) examined 138 females between 51 and 60 years of age who lived on farms in a cadmium-polluted area of Japan and 40 reference women in the same age group. Cadmium exposure was estimated from data on cadmium concentrations detected in the individual's farm's rice production (<0.1 to >0.7 μg Cd/g rice, wet weight) and on individual residence times (5 to 60 years). Possible cadmium exposure from consumption of river water (the river was polluted by discharges from a lead and zinc mine) was also taken into account (a maximum value of 9 ng Cd/g was reported in river water in 1967). Average urinary cadmium levels were approximately double in the exposed group (16.7 μg/g creatinine) when compared with the reference group (8.8 μg/g creatinine). Cadmium blood levels among the exposed persons were as high as 62 ng/g; blood samples were not obtained from the reference group.

Table VI-2 Counterimmunoelectrophoretic Analysis of Urinary Proteins in an Itai-Itai Patient

Molecular weight	Composition of fraction
54×10^3	immunoglobulin G albumin transferrin α_1-acidglycoprotein α^1-B-glycoprotein
45×10^3	Zn-α_2-glycoprotein α_2-HS-glycoprotein Bence-Jones protein (types λ and K)
21×10^3	apo-RBP (retinol binding protein free of retinol) holo-RBP (retinol binding protein plus retinol)
12×10^3	β_2-microglobulin

Adapted from Nomiyama et al. (1973).

Table VI-3 History and Renal Function Ranges in Seven Itai-Itai Patients

Symptom or test		Range of values
Age		60-79 years
Age of onset of disease		35-67 years
Urinary cadmium		3.1-19.8 µg/day
Urinary protein		37-107 mg/100 mL
Urinary amino acid		8.7-29.6 µmol/mL
Serum urea nitrogen		16-41 mg/100 mL
Urea clearance		9.9-46.2%
Creatinine clearance		7.5-42.5 mL/min
Renal plasma flow		50-260 mL/min
Filtration fraction		0.10-0.38
PSP test:	15 minute	1.6-17.2%
	120 minute	9.6-53.8%
Urine specific gravity		1.014-1.021
Osmolality:	plasma	297.0-321.5 mosm/kg
	urine	336.0-516.0 mosm/kg

Adapted from Nomiyama et al. (1973).

Urinary β_2-microglobulin excretion was measured quantitatively as an indicator of renal tubular changes; it should be noted, however, that the β_2-microglobulins in urine suggest but do not prove renal damage. The average urinary β_2-microglobulin excretion in the control and exposed groups was 75 and 900 µg/g creatinine, respectively. Increased β_2-microglobulin excretion was related to residence time in the exposed area as well as to the use of contaminated river water in the household. River-water exposure was accompanied by higher cadmium levels in blood as well as increased β_2-microglobulin excretion. However, any substantial cadmium exposure via river water probably occurred 20 to 30 years prior to these tests because of the present dams in the river and antipollution measures at the mine. Urinary β_2-microglobulin levels were about twice as high among river-water consumers as among the others. This finding may be a result of random variation. However, it seems that cadmium exposure via river water contributed considerably to the total cadmium dose. Among 35 women who lived at only one place within the exposed area and who had not consumed river water, there was a tendency toward slightly increased β_2-microglobulin excretion with an increased cadmium level in rice and increased residence time. There was also a correlation between cadmium levels in the blood and β_2-microglobulin excretion ($r = + 0.51$, $P<0.001$).

Nogawa et al. (1980) examined renal functions of all cadmium exposed inhabitants of a Japanese village over the age of 40 (96 subjects) and of a control group numbering 42. Creatinine clearance and percentage renal phosphorus reabsorption were selected as indicators of renal function. The findings from the urinary studies on the inhabitants in the cadmium polluted area are summarized in Table VI-4. Mean creatinine clearance and percentage renal phosphorus reabsorption values for men and women according to age groups are listed in Table VI-5. Creatinine clearance appears to decrease with increasing age, especially in the exposed group. The average renal phosphorus reabsorption values were lower in the cadmium exposed population. During the early stage of renal dysfunction, the decrease in creatinine clearance was much greater than the decrease in percentage renal phosphorus reabsorption. The great reduction in the latter occurred when creatinine clearance was below 50 mL/min. Creatinine clearance decreased as urinary β_2-microglobulin increased, although percentage renal phosphorus reabsorption did not fall until urinary β_2-microglobulin exceeded 100 mg/g creatinine. The same relationship was observed between creatinine clearance and total protein, as well as between percentage renal phosphorus reabsorption and total protein in urine. The authors suggest that creatinine clearance is a sensitive indicator of renal dysfunction caused by cadmium exposure. Reduction of creatinine clearance may occur at the early stage of chronic cadmium poisoning.

Roels et al. (1981a) investigated the relationship between environmental cadmium pollution and prevalence of signs of renal disturbance. The exposed group was comprised of sixty Belgian women (over 65 years-old with a mean age of 82.3 years and a mean duration of residence of 75.1 years) who had spent most of their lives in a cadmium-polluted area (Liege) but who had never been occupationally exposed to cadmium. One hundred-fifteen women (with a mean age of 81.2 years and a mean duration of residence of 72 years) living in two

Table VI-4 Prevalence of Renal Function Indicators in People Living in a Cadmium-Polluted Area

Parameters	Males N=34	Females N=38
Cadmium in urine, μg/g creatinine[a]	25.6	36.7
Prevalence of β_2-microglobinuria (∿4 mg/L and over), %	91.2	89.5
Prevalence of retinol binding protein (∿4 mg/L and over), %	79.4	68.4
Prevalence of proteinuria ($\geq$10 mg/dL),%	17.6	21.1
Prevalence of glycosuria ($\geq$20 mg/dL), %	32.4	31.6
Prevalence of aminoaciduria ($\geq$300 mg amino-N/g creatinine), %	23.5	44.7

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[a] Cadmium in urine of controls was 4.8 for men (N=22) and 10.0 for women (N=20).

Adapted from Nogawa et al. (1980).

Table VI-5 Mean Creatinine Clearance (Ccr) and Percentage Renal Phosphorus Reabsorption (% TRP) From Inhabitants of a Cadmium-Polluted Area and a Reference Area

		Inhabitants of polluted area			Inhabitants of reference area		
Sex	Age	N	Ccr[a]	% TRP[b]	N	Ccr[a]	% TRP[b]
Male	40-49	13	73.7±4.4	81.8±1.5	--	--	--
	50-59	20	69.4±5.3[c]	76.1±1.8[e]	7	99.1±8.4	86.5±1.1
	60-69	8	69.4±11.9	73.0±4.9[d]	10	72.5±9.7	87.4±1.9
	70+	6	64.6±10.6	70.4±4.7	5	96.4±12.7	83.2±2.3
Female	40-49	11	78.4±6.3	84.1±1.9	--	--	--
	50-59	20	65.3±3.0[e]	85.3±1.1	5	96.4±5.3	88.6±1.1
	60-69	12	44.8±4.4[c]	70.7±5.0[c]	7	75.5±9.5	89.7±1.1
	70+	6	54.3±2.6[d]	77.1±3.9[d]	8	80.8±8.0	90.5±1.1

[a] Mean creatinine clearance (mL/min).
[b] Percentage renal phosphorus reabsorption.
[c] Significant difference ($P<0.01$) compared to the control.
[d] Significant difference ($P<0.05$) compared to the control.
[e] Significant difference ($P<0.001$) compared to the control.

Adpated from Nogawa et al. (1980).

areas less polluted with cadmium (Brussels and Charleroi) served as the control group. The elderly women from the Liege area had increased excretion of cadmium in the urine compared to the group of aged women in the other two areas. The parameters selected for evaluating renal function followed the same trend. A statistically significant correlation was found between the urinary excretion rate of cadmium and that of total protein, amino acids, β_2-microglobulin and albumin. The results of this study (summarized in Table VI-6) suggest that general environmental pollution by cadmium, as found in some industrialized areas in Europe, may exacerbate the age-related decline of renal function in population groups nonoccupationally exposed to heavy metals. A retrospective epidemiologic study is needed to evaluate whether such exposure is responsible only for subclinical signs of intoxication or may lead to an increased morbidity and/or mortality by renal insufficiency. Furthermore, establishment of cadmium accumulation levels in tissues (especially liver and kidney) of people residing most of their lives in a polluted area is necessary to define the critical body burden of cadmium in the general population. This study may suggest that the critical level of cadmium in urine is much lower in elderly persons with progressively declining kidney function than that expected for middle-aged male workers. It is apparent that there is a need for additional data in order to refine the definition of the critical body burden of cadmium in the general population.

Roels et al. (1981b) measured the cadmium concentration in liver and kidney via in vivo neutron capture gamma-ray analysis in 309 male employees of two Belgian zinc-cadmium plants. Blood cadmium levels and the urinary

Table VI-6 Renal Toxicity Parameters in Women Living in a Cadmium-Polluted Area (Liege) and in Reference Cities (Brussels, Charleroi)

Parameter	Liege (N=60)	Brussels (N=45)	Charleroi (N=70)
Blood cadmium (μg/100 mL)[a]	0.16	0.06	0.12
Urinary cadmium (μg/h)[a]	0.093	0.055	0.040
Prevalence urinary cadmium (%)			
≥0.05 μg/h	76.7	53.3	22.9
≥0.10 μg/h	36.7	6.7	5.7
Proteinuria (mg/h)[a]	17.34	10.53	8.30
Prevalence proteinuria (%)			
≥10 mg/h	50.0	42.2	20.0
≥15 mg/h	36.7	20.0	11.4
Aminoaciduria (mg α-N/h)[a]	5.45	4.09	4.35
Prevalence aminoaciduria (%)			
≥7.5 mg α-N/h	18.3	0	5.7
β_2-microglobulinuria (μg/h)[a]	93.6	44.3	22.0
Prevalence $\beta_2$microglobulinuria (%)			
≥20 μg/h	25.0	22.2	14.3
≥50 μg/h	18.3	15.6	7.1
≥100 μg/h	10.0	6.7	2.6
Albuminuria (mg/h)[a]	1.54	1.18	1.52
Prevalence albuminuria (%)			
≥1 mg/h	30.0	31.1	18.6
≥2 mg/h	15.0	11.1	11.4

[a] Values reported are means.

Adapted from Roels et al. (1981a).

excretion of β_2-microglobulin, albumin, total protein, calcium and cadmium were also measured. Of the 264 subjects retained for the statistical analysis, 236 still worked at the plants and 28 others were retired cadmium workers or workers removed from cadmium exposure. The working group included 149 subjects with normal renal function who were engaged in jobs not directly related to cadmium production. The eighty-seven other workers were occupied with daily cadmium production; of these, 15 had sign(s) of renal dysfunction and 72 did not. The retired group was subdivided into 18 subjects with renal dysfunction and 10 subjects without.

Examination of the cumulative frequency distributions and the correlations between the various biological parameters in the different subgroups led the authors to several concluding observations: (a) calciuria did not vary much among the subgroups; (b) blood cadmium levels mainly reflect recent exposure to cadmium when there is no cadmium-induced renal damage; (c) urinary cadmium levels reflect the body burden of cadmium but increase in workers with renal dysfunction, particularly when signs of tubular dysfunction are present; (d) cadmium content of the liver is proportional to duration and intensity of cadmium exposure in workers with or without renal dysfunction; (e) renal cortical cadmium levels are higher in active production workers and in retired workers without renal dysfunction than in active non-production workers but are similar for cadmium workers with and without renal dysfunction. This similarity is a result of a progressive decrease in renal cortical cadmium after the onset of the renal damage. This hypothesis was supported by the following observations: (a) in retired workers with renal dysfunction, renal cortical cadmium correlates negatively with years of past exposure to cadmium (r=-0.59); (b) active cadmium production workers with renal dysfunction and retired workers with renal dysfunction excrete significantly (no P value given) more cadmium in urine than exposed workers without renal dysfunction; and (c) exposed workers with renal dysfunction have a decreased renal cadmium content (judged by the ratio of renal cortex cadmium to liver cadmium) in comparison with active cadmium production workers without renal dysfunction. Thus, the concentrations of cadmium in body tissues and fluids are complex functions of exposure, age and injury.

The authors suggest that their findings indicate a critical range of renal cortical cadmium levels of approximately 160 to 285 µg/g. The probability is very high that all persons with renal cortical cadmium concentrations greater than 285 µg/g, will show signs of renal dysfunction. Kidney dysfunction was found to be likely to develop in workers with liver cadmium concentrations between 30 and 60 µg/g; almost all the workers with levels greater than 60 µg/g in liver have renal dysfunction. In the absence of kidney dysfunction, urinary cadmium levels were shown to correlate with body burden of cadmium, but blood cadmium does not. On the basis of the interrelationships among cadmium concentrations in liver, kidney cortex, and urine, and the indicators of renal function, the authors concluded that the probability that male cadmium workers will develop cadmium-induced renal dysfunction appears to be very low when the critical urinary cadmium level of 10 µg/g creatinine is not regularly exceeded. At this urinary cadmium concentration the average cadmium body burden is 160 to 170 mg.

Ghose et al. (1981) presented a case report of a 37-year-old male worker who had been employed in a nickel/cadmium factory for five years. The subject smoked 30 cigarettes per day and neglected general protective safety rules regarding cadmium exposure. Results from routine clinical and biochemical tests were normal. Neutron activation measurement of kidney and liver indicated cadmium concentrations of 39 ± 4 mg (400 μg/g wet weight in renal cortex) and 8 ± 3 μg/g, respectively. Blood (28.3 μg/L) and urine (14.4 μg/g creatinine) cadmium concentrations were raised. However, renal function was effectively normal when assessed via glomerular filtration rate, renal plasma flow, serum creatinine, protein and β_2-microglobulin. The authors propose that a preferential induction of renal metallothionein relative to hepatic metallothionein avoided renal dysfunction by the low cadmium accumulation in the liver and a correspondingly negligible transport of the nephrotoxic cadmium-metallothionein complex from the liver to the kidney. They suggest that conditions of exposure and the relative amounts of cadmium in the liver and kidney must be considered in the concept of a critical renal cortical cadmium concentration.

Definition of a critical concentration of cadmium in the renal cortex has been debated at some length. It is clear that the critical level in any one individual may vary with many factors, including the nature of the exposure, climate, diet, sex, etc. This fact may account for the considerable range of critical concentrations reported by different authors. The problem was recently reconsidered by Kjellstrom et al. (1984), who suggested that a more useful concept would be that of the population critical concentration (PCC). A reanalysis of the published data indicated that the PCC-10 (the level which will be critical for 10% of an exposed population) is likely to fall into the range of 180 to 220 μg Cd/g fresh weight of renal cortex; the PCC-50 is likely to be about 25% higher.

2. Effect on the Liver

The liver accumulates large amounts of cadmium during chronic exposure. Liver dysfunction, however, has not been a common finding in exposed workers. Friberg (1950) found that the Takata reaction was positive in two and the thymol test in three of 19 workers exposed to cadmium oxide dust with a mean exposure time of 20 years. Increases in serum gamma globulin levels were found in several workers. While studies in rats indicate that some liver enzymes may be influenced by cadmium concentrations of the same magnitude as found in normal human adults (Sporn et al. 1970), it is unclear to what extent these findings can be applied to the human liver (Friberg et al. 1974). Thus, the commonly used clinical tests for liver function may not be suitable for evaluation of cadmium exposure.

3. Effect on the Bones

Osteomalacia and osteoporosis with tendency to fracture, bone deformation accompanied by lumbar pains, leg myalgia, pains on bone pressure, and disturbance of gait have been described in Itai-Itai patients (principally in postmenopausal women who have borne several children). Tsuchiya (1969a,b) discusses the clinical details of Itai-Itai disease emphasizing the following features: (1) pain of the back and/or shoulders and/or other bones with neuralgia-like pain of the thigh and/or upper arm; (2) waddling gait; (3) fractures and shortening of height; (4) increased alkaline phosphatase with decreased phosphorus and normal calcium concentration in serum; (5) positive proteinuria and glycosuria; and (6) bone changes by X-ray such as bone atrophy (high grade), bone healing zones, deformation of pelvis and femur and fish vertebra. Nutritional factors, particularly calcium and vitamin D deficiency, are thought to exacerbate the disease (Friberg 1974, CEC 1978). Friberg (1950) made a roentgenological study of the bones of 11 Swedish workers exposed to cadmium dust for 9 to 34 years, but found no abnormal changes. The intake of calcium and vitamin D is much higher in Sweden than in Japan; moreover, the Japanese had poor nutritional conditions during World War II. In exposed subjects, the levels of calcium and inorganic phosphorus in serum are often low, while the alkaline phosphatase level is generally high (CEC 1978). The same type of bone lesions seen in Itai-Itai have been found in some workers exposed to cadmium oxide dusts and fumes. Scott et al. (1980) measured total body calcium by neutron activation analysis in cadmium-exposed workers and reported an increased calcium deficit.

4. Effect on the Nervous System

Nervous system symptoms have been reported in Russia by Vorobjeva (Friberg et al. 1974) after an investigation of 160 workers in an accumulator factory. Subjective symptoms consisted of headache, vertigo, and sleep disturbances. Physical examination revealed increases in knee-joint reflexes, tremor, dermographia, and sweating. Subjects reporting these signs exhibited altered performance in sensory, dermal, optic and motor chronaxia tests.

5. Effect on the Hematopoietic System

A moderate anemia has been described in workers exposed to cadmium oxide dusts and fumes (Tsuchiya 1967). Blood examination in Itai-Itai patients usually reveals hypochromic anemia. Serum iron levels are low in many of these patients and some have elevated erythrocyte sedimentation rates. Almost no deviation from the normal has been observed in serum protein and albumin/globulin ratios (Murata et al. 1970).

6. Effect on the Cardiovascular System

Cadmium has been implicated as a factor that may cause hypertension in humans. A high cadmium body burden resulted in hypertension in some studies (Friberg 1974, CEC 1978). Conclusions regarding causality in these studies are frequently difficult to make due to a lack of adequate information regarding other important variables such as smoking habits, previous history and course of the disease. There are no reports showing that workers exposed to cadmium have a higher prevalence of hypertension than other groups (CEC 1978). In areas of Japan where extensive exposure to cadmium occurred for decades, hypertension has not been associated with cadmium (Friberg et al. 1974). It should be indicated, however, that the incidence of hypertension in the general population of Japan is also higher than that observed in the United States.

Schroeder (1965) used world-wide data on various trace metals in tissues of 358 adult subjects (187 from the continental U.S. and 171 from other nations) to explore the relationship of renal cadmium concentration to hypertension. The mean renal cadmium concentration was significantly higher ($P<0.05$) in subjects dying from hypertensive complications than in those dying because of accidents or arteriosclerotic heart disease. Results are summarized in Table VI-7.

Glauser et al. (1976) compared ten normal humans (mean age = 30.9 years) with a blood-cadmium level of 3.4 ng/mL, with a matched group of 17 untreated hypertensive subjects with a mean blood cadmium of 11.1 ng/mL. All of the normal subjects had blood cadmium levels below 8.0 ng/mL while 13 of the 17 hypertensive patients had blood cadmium levels above 8.0 ng/mL. The means for the two groups were statistically different ($P<0.001$). Dally et al. (1978) also examined the relationship between blood cadmium levels and hypertension in humans. Data from 29 matched pairs of men, 25 to 65 years-old, with untreated hypertension of unknown etiology, but without renal failure, were compared to normotensives. They found no significant difference in blood cadmium levels between patients and controls. The two groups were matched for age (mean of 51.5 ± 1.7 versus 50.3 ± 1.9 years), and smoking habits (mean of 18 ± 3 cigarettes/day versus 19 ± 3), but not for blood cadmium concentrations (mean of 3.3 ± 0.4 ng/mL versus 2.6 ± 0.4 ng/mL). An insignificant correlation was found for blood cadmium with the number of cigarettes smoked per day ($r=0.22$, $P<0.10$). A significant positive correlation between increasing age and blood cadmium was also noted ($r=0.28$, $P<0.05$). These and similar studies have been criticized for the use of blood as the biologic fluid for determination of cadmium in the kidney and whole body.

Table VI-7 Mean Cadmium and Cadmium/Zinc Ratios (± SEM) in Human Kidneys (Excluding Africa) According to Principal Cause of Death

Cause of death	No. of cases	Mean age (yr)	Cd (ppm ash)	P[a]	Cd/Zn Median	Cd/Zn Mean	Cd/Zn P[a]
U.S. Mainland							
Hypertension	17	50.9	4,220±390	--	0.79	0.77±0.0490	--
Accidents	117	42.0	2,940±120	<0.0005	0.60	0.62±0.0202	<0.01
Arteriosclerotic heart disease	27	56.2	2,660±270	<0.0005	0.60	0.62±0.0366	<0.01
Miscellaneous	26	47.1	3,380±350	n.s.[b]	0.54	0.58±0.0824	<0.01
Total	187						
Foreign							
Hypertension	17	45.6	5,080±830	--	0.94	1.00±0.1222	--
Accidents	23	33.8	3,170±830	<0.025	0.66	0.67±0.0604	<0.005
Arteriosclerotic heart disease	12	64.4	2,430±370	<0.01	0.49	0.48±0.0594	<0.005
Other cardiovascular disease	10	41.5	3,300±740	n.s.[b]	0.54	0.60±0.0938	<0.01
Malignant disease	32	48.0	3,540±400	<0.025	0.50	0.53±0.0669	<0.005
Chronic infections	15	42.4	3,580±600	n.s.[b]	0.48	0.58±0.1025	<0.025
Miscellaneous	10	34.6	2,810±390	<0.025	0.54	0.58±0.0824	<0.01
Total	119						

[a] P is probability of the difference between value reported and that of hypertension being due to chance.
[b] n.s. = Not significant. There were no significant differences between groups from U.S. mainland or foreign areas, except for the ratios of foreign accidents and arteriosclerotic heart disease ($P<0.05$).

Adapted from Schroeder (1965).

Cummins et al. (1980) conducted an *in vivo* study of renal cadmium concentrations in hypertensives using the non-invasive method of partial body neutron activation analysis. Sixty subjects with no history of industrial exposure to cadmium were selected for study. Thirty had long-standing histories of hypertension, severe enough to require treatment and 30 were matched controls. The hypertensive and control groups were matched with respect to age (mean of 58.9 versus 58.6 years), smoking (mean of 33.9 versus 29.1 pack years), renal function tests of creatinine (mean of 92 versus 82 µmole/L) and β_2-microglobulin (mean of 57.6 versus 41.5 µg/liter). The *in vivo* results obtained for the left kidney showed no significant difference between the hypertensive and the control groups. The hypertensive patients, however, were receiving medications (such as diuretics) which might have lowered their renal cadmium content below that for untreated hypertensives. The study confirmed elevated cadmium content in smokers as previously reported by Ellis et al. (1979). The data from the study are summarized in Table VI-8.

Lener and Bibr (1971) analyzed the kidney cadmium content at autopsy of 12 men 58 to 65 years-old (mean = 61.6 ± 1.4) who died of hypertensive disease and ten men 45 to 60 years-old (mean = 58.8 ± 1.5) killed in accidents. The cadmium content in the hypertensive men and controls was 36.11 ± 2.87 and 27.02 ± 3.13 µg/g wet weight, respectively. None of the subjects had been occupationally exposed to cadmium. The difference between the levels is statistically significant ($P<0.05$).

McKenzie and Kay (1973) reported on the 24-hour urinary excretion of cadmium, zinc and copper in 107 normotensive and 95 hypertensive women on

Table VI-8 Mean Renal Cadmium in Patients and in Controls

	No. of pairs	Hypertensive patients		Control subjects		Difference control patient	
		mg^{a}	μg/g^{b}.	mg^{a}	μg/g^{b}	mg^{a}	μg/g^{b}
All pairs	30	3.3 (SD 2.3)	29.5 (SD 28.3)	4.4 (SD 2.7)	37.8 (SD 27.4)	1.1 (SEM 0.6) n.s. ($P>0.05$)	8.3 (SEM 6.9) n.s. ($P>0.05$)
Never smoked	13	2.4 (SD 2.5)	20.3 (SD 16.7)	3.9 (SD 1.2)	34.5 (SD 16.6)	1.5 (SEM 0.7) $P<0.05$	14.2 (SEM 5.1) $P<0.02$
Smokers and ex-smokers	15	4.0 (SD 3.0)	38.9 (SD 34.6)	4.2 (SD 3.1)	37.5 (SD 34.8)	0.2 (SEM 0.8) n.s. ($P>0.05$)	-1.4 (SEM 12.3) n.s. ($P>0.05$)

[a] Total cadmium/kidney.
[b] μg Cd/g kidney.

Adapted from Cummins et al. (1980).

antihypertensive medications. A greater urine volume and 24-hour excretion of cadmium and copper was found in the hypertensive subjects than in controls. Cadmium was positively correlated with urine volume in both normotensive controls and hypertensives, but the greater mean urine volume of hypertensives compared to controls could attribute to their greater cadmium output. However, analysis of cadmium output, correcting for the volume difference, gave a statistically significant adjusted mean of 25 ± 16 μg Cd/24-hours in the normotensive control group and 31 ± 14 μg Cd/24-hours in the hypertensive group. The rate of cadmium excretion in hypertensives (0.024 ± 0.016 μg/min) was significantly greater than that found in controls (0.018 ± 0.014 μg/min). The cadmium/zinc ratio in urine was also markedly different between hypertensive (0.112 ± 0.114) and control (0.078 ± 0.082) subjects. No difference in cadmium output was evident between smokers and nonsmokers or between light and heavy smokers. Multi-drug therapies made useful analysis of specific drug-related changes impossible. The results of the study are summarized in Table VI-9.

An inverse correlation between the prevalence of cardiovascular diseases and the hardness of drinking water has been reported. Since hard water usually contains fewer heavy metals, cadmium in particular, than soft water, some studies have found a correlation between cadmium content and the prevalence of hypertension (CEC 1978). Bierenbaum et al. (1975) reported the reverse of this situation in the twin Kansas cities. Kansas City, Kansas, has water which is twice as hard as the softened water of Kansas City, Missouri (189 versus 78 mg/L as calcium carbonate) with the same source. In serum

Table VI-9 Urinary Excretion of Cadmium, Zinc and Copper by Control and Hypertensive Women

Subjects	Age (years)	24-hour urinary excretion Volume (mL)	Cd (µg)	Zn (µg)	Cu (µg)
Normotensive Control with BP 150/90 mmHg or less	43 ± 8[a] (107)	1,330 ± 460 (107)	23 ± 21 (106)	407 ± 187 (107)	55 ± 39 (68)
Control with BP above 150/90 mmHg	48 ± 7[b] (20)	1,344 ± 400 (20)	25 ± 20 (20)	370 ± 146 (20)	105 ± 94[c] (10)
Hypertensive	50 ± 8[d] (95)	1,552 ± 659[c] (95)	32 ± 23[e] (90)	412 ± 240 (95)	138 ± 144[c] (26)

[a] Values are mean ± standard deviation. Numbers of subjects are in parentheses.
[b] $P<0.02$.
[c] $P<0.01$ Statistical significance (t test) of mean difference compared
[d] $P<0.001$ to normotensive controls

[e] $P<0.02$ statistical significance (Mann Whitney U test) of mean difference compared to normotensive controls.

Adapted from McKenzie and Kay (1973).

studies conducted on matched groups of 260 adults averaging 37 years of age from each of the sample cities, serum cholesterol and triglyceride levels were found to be similar. Blood pressure, however, was significantly higher in Kansas City, Kansas, (128.6 ± 1.06 versus 121.1 ± 0.77 mm Hg systolic, $P<0.01$; 83.1 ± 0.81 versus 77.5 ± 0.52 mm Hg diastolic, $P<0.01$), as was serum sodium (140.60 ± 1.10 versus 138.59 ± 0.77 meq/L, $P<0.05$), while serum potassium was significantly lower (4.18 ± 0.05 versus 4.32 meq/L, $P<0.02$). Serum cadmium was more than ten times higher in Kansas (16.4 ± 6.3 versus 1.2 + 1.1 meq/L, $P<0.01$). Serum-calcium and magnesium levels were higher in Kansas, while copper, chromium, cobalt, and zinc were higher in Missouri. The total cardiovascular/renal mortality rate for white males aged 45 to 64 years was 36% higher in Kansas, the hard-water area, than in Missouri (799 versus 587 as rate/100,000). The design and analysis of this study have been criticized (CEC 1978).

Schroeder (1966) reported an inverse correlation of death rates (1960) from certain cardiovascular diseases by state with weighted average hardness of water. The correlation coefficients were significant ($P<0.005$) for hypertensive heart disease ($r = -0.415$ for males, -0.356 for females) and for arteriosclerotic heart disease ($r = -0.509$ for males, -0.364 for females). Statistical studies of death rates from 88 cities in the United States and levels of bulk and trace elements in municipal water supplies showed negative correlations for 12 major and 4 trace constituents. The purer the water in terms of dissolved elements, the higher the death rate was from cardiovascular disease. No trace elements (19 elements were measured), including cadmium, were highly correlated. One explanation of this phenomenon involves the corrosive quality of soft water on metal pipes in dwellings. However, the potential association of hypertension with water hardness is controversial and, as for air, the intake of cadmium via water is low (CEC 1978).

Masironi (1974) stressed data showing various human populations with significant differences (level of significance not specified in report) in renal cadmium concentrations. Renal cadmium levels of Caucasoid Americans, Europeans and Asiatics were higher than those of Negroid Africans and lower than those of Mongoloid Asiatics. This pattern is consistent with the epidemiology of hypertension, namely, that renal cadmium and blood pressure are low in Africa, south of the Sahara, and high in parts of eastern Asia, particularly Japan and Formosa.

7. Effect on the Pancreas

The effects of cadmium on pancreatic function have attracted almost no interest despite high concentrations detected in autopsy material from cadmium workers. Murata et al. (1970) examined 60 cases of Itai-Itai patients and noted an occasional condition resembling pancreatic diarrhea. The authors detected a tendency toward declined pancreatic functions, but did not cite specific tests or values.

C. Teratogenicity/Reproductive Effects

1. Teratology

No studies on teratology of cadmium-exposed women are known.

2. Testes

Smith et al. (1960) found high levels of cadmium in the testicles of men industrially exposed to cadmium fumes. No fibrosis or tubular atrophy was observed. Mitotic activity was normal, but maturation of spermatocytes to spermatids and spermatozoa was infrequent.

3. Fertility

Favino et al. (1968) investigated the fertility of ten cadmium workers and analyzed androgens in urine. One case of impotence with abnormally low testosterone levels in urine was found. The scope of this study was so limited as to make general conclusions difficult.

4. Perinatology

No studies on lactation or postnatal development of children born to cadmium-exposed pregnant women are known.

D. Mutagenicity

There is relatively little information on the mutagenic potential of cadmium in humans. Shiraishi et al. (1972) reported chromosomal aberrations in cultured human peripheral leukocytes induced by cadmium sulfide at 0.062 μg/mL culture fluid. The results are summarized in Table VI-10.

Shiraishi and Yosida (1972) obtained human peripheral leukocytes from seven Itai-Itai patients and examined them for chromosomal abnormalities (72-hour cultures). The data showed that the frequency of chromosomal abnormalities in all Itai-Itai patients was significantly higher than that of the control subjects. Chromatid breaks were a common abnormality in patients, whether these alterations were the result of permanent damage to the blood stem cells or a direct effect of circulating cadmium was not determined. The results of the study are summarized in Table VI-11.

O'Riordan et al. (1978) conducted chromosome studies on peripheral blood lymphocytes (48-hour cultures) from 53 male workers at a cadmium pigment factory. Forty of these men (17 to 61 years old) were actively engaged in pigment processing (6 weeks to 34 years occupational exposure); the remaining 13 workers (20 to 58 years old) were selected as on-site controls. The mean cadmium blood concentration in the exposed group was 1.95 μg/100 mL (range = < 0.2 to 14.0 μg/100 mL). Eight of the controls had cadmium concentrations of less than 0.2 μg/100 mL and five of the controls had a range of blood cadmium between 0.6 and 2.9 μg/100 mL. The atmospheric cadmium concentration had

Table VI-10 Chromosomal Aberrations and Their Frequencies in Human Leukocytes After Treatment with Cadmium Sulfide

Duration of treatment (h)	Total number of cells observed	Number of cells with chromatid breaks (%)	Number of cells with isochromatid breaks (%)	Number of cells with trans-location (%)	Number of cells with dicentric chromosomes (%)
0(control)	50	0	0	0	0
4	50	17(34)	2(4)	0	7(14)
8	50	7(14)	14(28)	6(12)	3(6)

Adapted from Shiraishi et al. (1972).

Table VI-11 Types and Frequencies of Chromosomal Aberrations Observed in Itai-Itai Patients and in Normal Control Subjects

Age and sex	Total No. of of cells observed	No. of cells with single chromatid breaks	No. of cells with isochromatid breaks or gaps	No. of cells with chromatid translocations	No. of cells with dicentric or dicentric-like chromosomes	No. of cells with acentric fragments	Total No. (%) of cells with chromosome abnormalities
Controls							
58-F	50	1	0	0	0	0	1(2)
62-F	50	0	0	0	0	0	0(0)
67-F	50	0	0	0	0	0	0(0)
70-F	50	1	0	0	0	0	1(2)
70-F	50	0	0	0	0	0	0(0)
78-F	50	0	0	0	0	0	0(0)
Itai-Itai disease							
52-F	50	15	2	8	2	3	30(60)
66-F	50	18	3	6	0	1	28(56)
69-F	50	14	3	6	0	0	23(46)
69-F	50	6	1	0	0	0	7(14)
70-F	50	19	3	7	1	2	32(64)
70-F	50	12	2	3	2	1	30(60)
73-F	50	15	2	6	1	3	27(54)

Adapted from Shiraishi and Yosida (1972).

ranged around 0.6 to 1.0 mg Cd/m^3 but at the time of the study had been lowered to 0.2 mg Cd/m^3. Two of the men in the exposed group had clinical tubular-type proteinuria. Analysis of the data did not reveal any consistent or significant (P-value not given) differences in the incidences of chromosome- or chromatid-type aberrations between the two groups of men and a group of control males drawn from another study. No significant correlations were found between the extent of chromosomal damage detected, the worker's occupational history, or the individual's blood cadmium concentration. The data are summarized in Table VI-12.

Studies by Deknudt and Leonard (1975) on 23 industrial workers who had a mean cadmium blood concentration of 3.16 µg/100 mL (range = 0.60 to 17.90 µg/100 mL) and an average exposure time of 12 years to high cadmium and lead concentrations showed a small but significantly ($P<0.02$) higher yield of complex chromosomal anomalies (48-hour cultures); however, there was no correlation between degree of exposure and aberration yield.

Bui et al. (1975) studied four female Itai-Itai patients and five male workers from an alkaline battery factory and found no increase of aberrations in lymphocytes (48 and 72 hour cultures). Thus, the results of the studies conducted on mutagenicity are somewhat contradictory.

E. Carcinogenicity

Potts (1965) reported the prevalence of cancer among 74 workers exposed to cadmium oxide dust in the production of alkaline batteries. Among the men

Table VI-12 Aberration Frequencies in Peripheral Blood Lymphocytes (48-Hour Cultures) of Workers Exposed to Cadmium, On-site Controls and a "General Population" Control

			Cells with chromatid aberrations			
No. of men studied	Total cells scored	Normal cells	Total No.	Gaps	Breaks	Inter-changes
Group 1, Cd exposed 40	3,740	3,490 (93.42%)	158 (4.22%)	156 (4.17%)	2 (0.053%)	4 (0.107%)
Group 2, Cd control 13	1,243	1,154 (92.48%)	38 (3.06%)	37 (2.98%)	1 (0.080%)	0
Gen. pop., control 285	3,107	-- (96.66%)	68 (2.18%)	65 (2.09%)	4 (0.129%)	0

Adapted from O'Riordan et al. (1978).

with at least ten years exposure to cadmium, eight had died. The years of exposure and cause of death are presented in Table VI-13. There was a high prevalence of proteinuria and anosmia in the workers. No control group was examined.

Kipling and Waterhouse (1967) examined 248 employees and former employees exposed to cadmium oxide and nickel hydroxide for at least one year. The observed number of cases of carcinoma of the prostate (four cases) was significantly ($P<0.01$) in excess of the expected number (0.58 cases). The total number of cancer cases (12) for all body sites was small. The incidence and type of cancer are presented in Table VI-14. The four men (age: 51 to 75 years) that died from prostatic cancer had also been exposed to nickel hydroxide, powdered nickel and ferric hydroxide; however, there have been no reports of prostate cancer among nickel workers. Holden (1969) reported one case of carcinoma of the prostate and one of the bronchus among 42 men exposed to cadmium fumes from 2 to 40 years.

Morgan (1969, 1970, 1971) studied the renal and hepatic cadmium levels for different disease groups at autopsy. Cadmium concentrations in a group of male patients who had died from bronchogenic carcinoma were compared with a control group and a group who had died from other forms of neoplasia. The average cadmium concentrations (μg/g ash ± SD) in the group who had died of bronchogenic carcinoma (average age: 60 years) were statistically higher ($P<0.05$) than those in other groups. The data are presented in Table VI-15. A detailed examination of the groups divided by those with bronchogenic

Table VI-13 Types of Cancer Observed in Cadmium Workers

Year of death	Age	Cd exposure in years	Cause of death
1960	65	31	Auricular fibrillation
1960	75	14	Carcinoma of prostate
1961	65	37	Carcinoma of prostate
1962	63	34	Bronchitis and atheroma
1962	78	18	Bronchitis
1963	53	35	Carcinoma of bronchus
1964	65	38	Carcinoma of prostate
1964	59	24	Carcinomatosis

Adapted from Potts (1965).

Table VI-14 Incidence of Carcinoma in a Group of Men Exposed to Cadmium

Site of Cancer	Incidence Expected	Incidence Observed
All sites	13.13	12
Bronchus	4.40	5
Bladder	0.51	1
Prostate	0.58	4
Testes	0.11	0

Adapted from Kipling and Waterhouse (1967).

carcinoma with or without emphysema and those with only emphysema revealed elevated renal cadmium level in all groups. The emphysema only group had hepatic and renal cadmium concentrations of 290 and 2,921 μg/g ash relative to control concentrations of 170 and 2,512 μg/g ash, respectively. The author suggested that elevated cadmium levels are probably related to smoking habits.

Kolonel (1976) reviewed malignancies obtained from Roswell Park Memorial Institute records covering the period from 1957 to 1964 for white males from 50- to 79-years-old to assess prior exposure to cadmium. The results suggest an association between renal cancer and exposure to cadmium and a synergistic effect between occupational exposure and smoking. The relative risk for men who both smoked and worked in high-exposure occupations (e.g., Table VI-15 electroplating, alloy-making, welding, storage battery manufacturing) was four times that for men who did neither.

Lemen et al. (1976) conducted a retrospective cohort mortality study of 292 male workers who had been employed in a cadmium plant for a minimum of two years. Gross cadmium air concentration, in general, ranged below 1 mg/m^3. There were greater deaths from total malignancies (27 versus 17.57 expected), lung cancer (12 versus 5.11 expected) and prostatic cancer (4 versus 1.15 expected) among the cadmium smelter workers than would be expected in the general population. The authors concluded that their observations implicated cadmium exposure as a cause of certain types of malignant disease. It was also noted that mortality from cardiovascular disease was significantly lower among the cadmium workers (24 versus 43.52 expected).

Table VI-15 Concentrations of Cadmium in Liver and Kidneys (μg/g ash) in Patients Dying from Cancer of the Lung and Other Forms of Cancer and in Controls

Cancer	N	Liver	Kidney
Lung	47	254±133	3,513±1,587
Other forms	50	179±140	2,937±2,065
Control	55	182±99	2,406±1,299

Adapted from Morgan (1970).

Many epidemiological studies on cadmium-exposed workers have shown excess death due to prostatic cancer. Reported cases probably had considerable exposure to cadmium decades earlier, but insufficient data exist to permit any dose-response calculations. The general epidemiology of prostatic cancer was not taken into account in any of the studies. Piscator (1981) reviewed the role of cadmium in carcinogenesis with special reference to cancer of the prostate. He noted that racial, sexual, marital and nutritional status are all important influencing factors in prostate cancer. Based on his review of the literature, Piscator (1981) suggested that direct action of cadmium on prostatic cells is not likely, nor is it probable that low level exposure to cadmium is a causative factor for prostatic cancer. Data were summarized from several studies which examined: (1) cadmium and zinc in the prostate; (2) cadmium levels in kidney, liver and testicles from normal men; (3) cadmium levels in the prostate of men with benign prostatic hypertrophy or prostate cancer; and (4) cadmium levels in the prostate, liver, kidney and testicles of occupationally- and environmentally-exposed men (see Table VI-16).

Despite relatively high environmental levels of cadmium, death from cancer of the prostate is uncommon in Japan, although there has been a 4-fold increase in prostatic cancer mortality from 0.5 to about 2 per 100,000 between 1950 and 1963. However, the incidence of prostate cancer in Japan is still 6 to 11 times less than that in the United States (Piscator 1981).

F. Summary

Acute human cadmium poisoning is usually the result of ingestion of food or liquid which has been stored in cadmium-plated vessels. Oral ingestion of

Table VI-16 Cadmium and Zinc in Prostate and Cadmium in Kidney, Liver and Testicles from Normal Men, Men with Benign Prostatic Hypertrophy, Cancer of the Prostate, Men Exposed to Cadmium in the General Environment and Occupationally Exposed Men

			Metal conc. (mg/kg dry weight)				
			Prostate		Kidney	Liver	Testicles
Group	Age	N	Cd	Zn	Cd	Cd	Cd
Normal	1	10	0.26	183	1.3	0.67	
	2-5	10	0.72	160	5.4	1.1	
	6-10	10	0.61	167	15	2.0	
	11-20	10	0.65	238	18	2.0	
	21-30	10	1.3	396	29	2.6	
	31-40	10	1.8	311	55	6.0	
	41-50	10	2.1	310	92	7.9	
	51-60	10	3.0	485	78	5.9	
	61-70	10	2.1	520	96	6.9	
	71-80	10	2.1	456	62	6.0	
	81-90	10	1.8	419	27	4.9	
	40-70	17			70	10	2.3
	40-80	20			133	13	4.1
	36	9	0.58	445			
	10-60	15			180	11	2.6
	49	1	0.90		40	7	0.95
	56	1	0.85		47	7	0.8
	56	1	0.50		60	10	1.0
Benign prostatic hypertrophy	41-90	?	1.1				
	70	23	2.58	449			
	?	15	0.61	555			
Cancer of the prostate	41-90	?	0.62				
	73	9	14.5	170			
General environment	83	1			270	317	70
Occupational exposure	46	1	185		500	550	170
	55	1	90		1,200	1,035	45
	67	1			550	224	3.5

Adapted from Piscator (1981).

3 mg is believed to have no adverse effects. Ingestion of higher doses (up to about 300 mg) produces sickness, symptoms of which include nausea, vomiting, diarrhea and muscle cramps. Severe poisoning is caused by ingestion of more than 300 mg, and symptoms include liver injury, renal failure, cardiopulmonary depression and death.

In humans, chronic low level cadmium ingestion in non-occupational settings does not result in adverse health effects except for Itai-Itai disease in Japan. The most prominent symptoms of Itai-Itai are bone abnormalities (osteomalacia, osteoporosis, bone pain, increased fractures), signs of renal disease (proteinuria, glucosuria) and a moderate anemia. The proteinuria observed is characterized by the excretion of low molecular weight proteins, suggesting impaired reabsorption in the proximal tubule. Glucosuria and aminoaciduria also reflect decreased tubular reabsorption. Creatinine clearance (an index of glomerular filtration rate) may also be decreased. Renal dysfunction is associated with increased renal cadmium content, but when the disease becomes severe, the cadmium content decreases, perhaps by desquamation of cadmium-containing tubule cells. It has been estimated that the concentration at which 10% of a population is likely to show signs of renal dysfunction (the PCC-10) is 180 to 220 μg Cd/g renal cortex. Individuals with values over 285 μg/g usually display signs of renal dysfunction.

Cadmium is suspected of being a risk factor in hypertension in humans, but this is a subject of some controversy. One problem in assessing whether a correlation exists between hypertension and cadmium is the criterion employed to determine cadmium exposure. Use of different criteria may yield different results. In addition, it is difficult to control and match the other known risk factors associated with human hypertension, and so it is perhaps not surprising that there is no universal agreement. Nevertheless, a number of extensive studies have found a significant correlation between hypertension and increased cadmium exposure.

Little information is available regarding the mutagenicity of cadmium in humans. Leukocytes exposed to Cd^{2+} (0.06 mg/L) in vitro for four to eight hours showed increased chromosomal abnormalities, and leukocytes from patients with Itai-Itai disease also showed chromosomal abnormalities. Lymphocytes, on the other hand, did not show chromosomal abnormalities after industrial exposure or in Itai-Itai disease.

No evidence exists that oral ingestion of cadmium is carcinogenic in humans. Several studies of cancer rates in workers exposed to cadmium fumes report increased incidence of lung, renal or prostate cancer, but the data are not sufficient to permit strong conclusions. Conversely, prostatic cancer rates are low in Japan, despite relatively high environmental cadmium concentrations.

VII. MECHANISMS OF TOXICITY

A. Mechanisms in the Kidney

Cadmium accumulates in the kidneys, but until renal injury occurs only small quantities are excreted in the urine (Friberg et al. 1974). Urinary cadmium excretion probably relates to the total body burden up to a certain or "critical" cadmium concentration in the kidney (around 200 μg/g wet weight of renal cortex). When the "critical" concentration is reached, the urinary cadmium excretion increases and the rate of cadmium accumulation in the kidney decreases. Friberg et al. (1974) proposed an hypothesis to explain published toxicity data from studies of chronic low-level cadmium exposures. They suggest that unbound cadmium accumulates in the kidneys when cadmium exposure exceeds available or bound metallothionein in renal tissue. Cadmium then exchanges with zinc and interferes with normal cellular metabolism.

The rate of cadmium accumulation in the kidney decreases and urinary cadmium excretion increases as renal function is disrupted because metallothionein reabsorption is impaired. Cadmium continues to be reabsorbed and cadmium tissue concentrations may increase. As the reabsorption defect becomes more severe, renal cadmium concentrations eventually decrease. Cadmium may also be excreted together with desquamated tubular cells further decreasing renal cadmium content. This hypothesis suggests an explanation for the paradoxical findings in histological examinations of autopsy tissues from chronic cadmium poisoning cases and biopsies from occupationally exposed workers. High renal cadmium concentrations are paradoxically associated with histologically normal kidneys, while relatively low renal cadmium concentrations are associated with long-standing proteinuria and gross structural renal changes. Thus, the more severe and long-lasting the renal lesion, the more cadmium is excreted.

Metallothionein is an integral component of the regulatory mechanism for zinc and cadmium metabolism (Foulkes 1982a). Oral or parenteral administration of either cadmium, zinc or other metals induces synthesis of metallothionein. The metallothionein mRNA content of polysomes quickly increases after cadmium or zinc enters into the cell. Poly (A^+) RNA is synthesized, followed by a concomitant increase in metallothionein biosynthesis and metal binding (Cousins 1979). The administration of cadmium-metallothionein is more toxic to the kidney tubule than is treatment with $CdCl_2$. The metallothionein-bound cadmium concentrates in the tubule to a greater extent and produces more urinary cadmium excretion than does free cadmium (Nordberg et al. 1975, Cherian 1979, Cherian et al. 1978). Thus, it has been suggested that metallothionein plays a role in elicitation of renal tubular impairment after chronic cadmium exposure (Nordberg et al. 1975).

The species of bound metal influences the degradation of the metallothionein complex. Cadmium-metallothionein is more resistant to breakdown *in vivo* and *in vitro* relative to zinc-metallothionein (Cousins 1979). When the polypeptide chains of cadmium-metallothionein degrade, the liberated cadmium ions are quickly incorporated into newly synthesized thionein. This explains the increase in cadmium content of the kidneys and liver with age and environmental exposure. Metallothionein binds zinc, cadmium and other metals, and thus this inducible protein provides a locus for interaction between different metals (Cousins 1979). While administered cadmium-metallothionein may act as a nephrotoxin under some experimental conditions, when synthesized within the cell it serves as a detoxification mechanism (CEC 1978).

The molecular mechanism of cadmium toxicity is unknown. It is appealing to suggest a mechanism involving displacement of zinc or other essential trace minerals by cadmium resulting in enzyme inhibition. Cadmium ions also react with tissue proteins to form insoluble metal proteinates (carboxyl groups) and stable metal mercaptides (sulfhydryl groups), causing an alteration in structure or a decrease in solubility sufficient to impair enzyme activity (Simon et al. 1947, Jacobs et al. 1956). The altered mitochondrial structures in the kidney reported by Nishizumi (1972) may be due to a cadmium-induced interference with oxidative phosphorylation and cellular metabolism. The diffuse scarring of peritubular capillaries, deposition of peritubular connective tissue fibers and constriction of small renal arteries observed in chronic cadmium feeding studies decreases renal circulation of blood and plays a contributory role in kidney dysfunction (Fowler et al. 1975).

Cousins (1979) suggests a dynamic relationship among cadmium metabolism, distribution and toxicity with regard to metallothionein. As cadmium enters the intestinal mucosal cell, it probably helps to induce synthesis of intestinal metallothionein, which sequesters a major portion of the dietary cadmium that is absorbed by mucosal cells.

After absorption, cadmium is transported via the plasma to the liver where it is incorporated into hepatic metallothionein. Hepatic cadmium-thionein undergoes degradation, although more slowly than either thionein or zinc metallothionein. During this period cadmium can interact with other cellular components (Cousins 1979). Metallothionein may be the form in which cadmium is transported from liver to kidney (Johnson and Foulkes 1980), where eventually the major fraction of body cadmium is deposited, in large part as Cd-metallothionein.

Dietary calcium intake influences cadmium toxicity. Production of a calcium binding protein (CaBP) is substantially increased in the intestinal mucosal cells when dietary calcium intake is low. The CaBP is involved in absorption of dietary calcium. During periods of calcium restriction, when the synthesis of calcium-binding protein (CaBP) is increased, cadmium binds to the protein. This cadmium-binding activity of CaBP may help explain the increased accumulation of cadmium when dietary calcium intake is reduced (Cousins 1979).

The onset of renal damage is delayed following initiation of cadmium exposure, presumably due to the slow rate at which cadmium accumulates in renal tissue. One explanation for the latent onset of renal toxicity is that there is a critical concentration of cadmium in the renal cortex above which the toxic effects of cadmium are exerted within the cells. Cadmium is believed to reach the kidney from the liver in the form of metallothionein. The liver or other organs release cadmium-thionein when the cadmium tissue burden becomes excessive. Although higher concentrations of thionein can be detected in plasma of cadmium-exposed workers versus control workers, a significant correlation between plasma thionein concentrations and the magnitude of cadmium exposure is not found. As a low molecular weight protein, cadmium-thionein is filtered through the glomerulus and subsequently reabsorbed by renal proximal tubule cells. As a result, cadmium-thionein is deposited specifically in one particular cell-type (the proximal tubule cell) of the kidney. The proximal tubule cell is the target cell in cadmium-thionein toxicity.

In ultrastructural studies, only the proximal tubule cells show evidence of morphological changes after cadmium-thionein treatments, while distal tubule cells and glomeruli appear unchanged. Changes in proximal tubule cells initially include vesiculation and an increase in small apical lysosomes. These changes progress until cell death and desquamation occur, probably due to an inhibition of RNA synthesis and other biochemical functions. The toxic effect of cadmium-thionein on proximal tubules is also indicated by the low molecular weight proteinuria that develops rapidly after treatment as a consequence of decreased tubular resorption of filtered proteins. Presumably, the cadmium ion is the toxic moiety in cadmium-thionein toxicity, following degradation of the metal-protein complex. On the basis of this hypothesis, the route by which cadmium enters the renal cell is not as important to the determination of its toxicity as are the rate at which it enters the cell and the overall concentration of unbound cadmium within the cell.

It is noteworthy that methylcadmium has been demonstrated to induce severe proteinuria in cats (Chang and Sprecher 1976). Aquatic microorganisms could possibly methylate cadmium (as occurs with mercury) suggesting a potential hazard from organocadmium (Chang and Sprecher 1976).

B. Mechanisms in the Liver

Means et al. (1979) examined the mechanism of hepatic microsomal monooxygenase inhibition in male Sprague-Dawley rats (age not specified) after a single ip injection (2 mg Cd^{2+}/kg) of cadmium acetate. The authors suggest an indirect action whereby adequate amounts of enzyme co-factors are reduced through alteration of turnover rates. These in vitro studies suggest that cadmium could interfere with a critical axial sulfhydryl ligand (presumably cysteine) to the iron in ferricytochrome P-450, leading to a conformational change in the protein moiety (P-450 to P-420); however, the concentrations of cadmium required to elicit such changes are approximately 100 times greater than the cadmium content of microsomes 48 to 72 hours after cadmium administration. In vivo, cadmium appears to exert its inhibitory effect on the hepatic microsomal monooxygenase system by decreasing the availability of cytochrome P-450. Krasny and Holbrook (1977) have reported that cadmium induces microsomal heme oxygenase, the first enzyme in the heme degradation pathway.

Glutathione is involved in the protection of the liver against a number of toxic compounds via conjugation reactions. There appears to be a relationship between hepatic glutathione concentrations and the hepatotoxicity of toxicants metabolized by the microsomal monooxygenase enzyme system. While cadmium is not metabolized by the liver per se, it readily accumulates in this vital organ where it could cause cell damage by combining with sulfhydryl group-containing cellular components such as microsomal drug-metabolizing enzymes. Dalvi and Robbins (1978) reported that acute intraperitoneal administration of $CdCl_2$ (3 mg Cd/kg) to male albino Swiss mice (age not specified) resulted in significant decreases in hepatic glutathione concentrations, benzphetamine metabolism and cytochrome P-450. They also reported that the incubation of 1 mM cadmium with mouse liver homogenate resulted in the inhibition of microsomal membrane lipid peroxidation (decreased malonaldehyde production).

Stacey et al. (1980) reported that 50 to 400 µM $CdCl_2$ incubated with hepatocytes isolated from male Sprague-Dawley rats (age not specified) significantly increased lipid peroxidation (increased thiobarbituric acid-reacting substances). There was also evidence of toxicity in the liver cell suspension with respect to membrane (loss of intracellular potassium ion and leakage of aspartate aminotransferase) and metabolic (increased lactate:pyruvate ratio) integrity. Several chelating compounds reduced intracellular accumulation of cadmium, cellular toxicity and lipid peroxidation. However, reduced toxicity was not consistently associated with inhibition of the lipid peroxidation response. Two different antioxidant compounds that inhibited the lipid peroxidation attributable to cadmium had no consistent protective effect against loss of intracellular potassium ion. The investigators concluded that cadmium toxicity in isolated rat hepatocytes can be dissociated from the concurrently observed lipid peroxidation, so the toxic response is apparently not caused by lipid peroxidation. They did not rule out the possibility that the toxic action may still be a direct membrane effect, such as binding of membrane sulfhydryl groups.

In an effort to overcome the difficulty of comparing dose-response relationships in other studies using various doses, routes of administration and experimental design, Eaton et al. (1980) examined the effect of cadmium on several hepatic cellular systems in a single study. Male Sprague-Dawley rats received two intraperitoneal doses of 5, 10 or 20 umol Cd/kg (as $CdCl_2$). Increased hepatic heme oxygenase activity, decreased hepatic P-450 levels, increased hepatic and renal metallothionein were dose-dependant responses. Cadmium did not affect reduced glutathione concentrations in liver or kidney. However, while acute exposure to cadmium clearly decreases cytochrome P-450, chronic exposure does not.

Kotsonis and Klaassen (1978) found that 100 mg Cd/L of drinking water administered to rats for 24 weeks had no effect on hepatic cytochrome P-450 content. They postulated that the lack of cytochrome P-450 depression in chronically exposed rats was a result of the protective effects of increased cellular content of metallothionein from the exposure period. Thus, acute studies reveal altered enzyme activity, such as induction of heme oxygenase activity; however, cadmium may not exert the same effect after repeated exposures.

Eaton et al. (1980) also found similar log dose-response profiles (slopes) for increased hepatic content of metallothionein with cadmium and zinc, whereas the relationship for lead was considerably less. This suggests that zinc and cadmium may share a similar mechanism for the increased hepatic content of metallothionein while lead induces the binding protein by a second, less effective mechanism.

Pence and Schnell (1979) found that intraperitoneal injection of 2 mg Cd/kg (as $CdCl_2$ in water) produced a marked decrease in drug metabolizing activity in liver microsomes from adult male Sprague-Dawley rats, but only a small effect in liver microsomes from female rats or sexually immature rats of either sex. Castration diminished the effects seen in adult males and administration of testosterone increased the effects in females. The authors concluded that sex-related differences in the inhibitory effect of cadmium on the hepatic microsomal monoxygenases in the rat are partially mediated through the toxic action of cadmium on androgen-dependent elements of the enzyme system.

The role of metallothionein in the accumulation and metabolism of cadmium has been discussed above. Ohi et al. (1981) have reported that poly(A)-containing 9.4S RNA from rat liver with an apparent molecular weight of 1.39×10^5 influenced the in vitro synthesis of metallothionein. They found that the specific activity of metallothionein-mRNA is at least four times higher in the liver RNA preparations after multiple injections of cadmium than after a single acute exposure. The authors suggest that the higher amount of metallothionein-mRNA in rats receiving multiple exposures to nontoxic doses of cadmium may be explained either as a stabilization of the mRNA, an enhanced rate of specific metallothionein gene transcription or stimulation of selective amplification of the metallothionein gene.

Singhal et al. (1974) found a stimulation of gluconeogenic pathways in livers of ten male Wistar rats (age not specified) following 45 daily intraperitoneal injections of 1 mg Cd/kg (as $CdCl_2$). Significant ($P<0.05$) increases in the four key enzymes of gluconeogenesis in the liver were observed, as follows: pyruvate carboxylase (141% of control), phosphopyruvate carboxylase (160%), hexosediphosphatase (126%) and glucose-6-phosphatase (169%).

C. Mechanisms in Bone

Cadmium does not accumulate to any considerable extent in osseous tissue, thus a direct toxic effect upon bone seems unlikely. While cadmium effects upon zinc metabolism, essential for bone tissue, cannot be ruled out, little data are available for deriving acceptable conclusions. Friberg et al. (1974) suggest that the secondary effects of cadmium on calcium-phosphorus metabolism is the most likely mechanism underlying cadmium-induced osteomalacia. Theoretically, cadmium exposure could influence metabolism of bone minerals in several ways: (1) by directly affecting the absorption of bone minerals and vitamin D in the gastrointestinal tract, especially in the case of oral exposure (malabsorption syndrome), (2) by changing parathyroid activity, or (3) by directly affecting the renal regulation of the calcium/phosphorus balance (renal osteomalacia). Cadmium can also inhibit vitamin D activation in *in vitro* kidney preparations and *in vivo* at higher concentrations (Cousins 1979). None of these possibilities has been ruled out entirely by the available data. Data relating to the effect of cadmium on parathyroid hormone, which regulates blood calcium concentrations by influencing bone resorption and renal excretion of phosphate, are equivocal, in part because parathyroid hormone will invariably be involved when disturbances in bone salt metabolism occur.

D. Mechanisms in the Cardiovascular System

Epidemiological studies have associated cadmium exposure with hypertension and high renal cadmium content. However, much of the data have been obtained by analyses of kidneys from humans who died from vascular disease with little or no information available regarding previous history, course of the disease or smoking habits, for example. Thus, firm conclusions regarding causality cannot be made.

Cardiovascular disease has also been associated with dustfall data or cadmium concentrations in air. Even at high ambient air concentrations, the estimated total amount of cadmium absorbed over a 50-year period would only amount to a small fraction of the total body burden. Various studies have not observed a higher prevalence of hypertension among cadmium workers or Itai-Itai patients (Friberg et al. 1974). However, an association between soft drinking water, which is corrosive to metal pipes and may dissolve cadmium and other metals, and cardiovascular mortality rates has been made in several studies but the relationship to cadmium is tenuous. Hypertensive effects of cadmium in animals have been reported, although results are strongly dependent on dose, duration of exposure, sex, species, strain and genetic background (Friberg et al. 1974).

Several mechanisms for cadmium-induced hypertension have been discussed in previous sections of this report; they include increases in cardiac output, cardiac catecholamines (inhibition of aortal MAO and COMT), circulating renin, sodium resorption and sodium retention (Perry and Erlanger 1974). Schroeder and Vinton (1962) postulated that cadmium may directly or indirectly act on vascular smooth muscle via the kidneys to raise blood pressure. The hypertensive effects of cadmium have also been related to kinin metabolism (reduced urinary excretion of kallikrein) which has been associated with genetic hypertension in rats (Petering et al. 1979). Kopp et al. (1980) suggest that their observations of cadmium-induced atrioventricular-nodal cell depression indicate a competitive displacement of membrane calcium or altered cellular uptake of calcium ions. They also postulate that the depressed contractility found in cadmium-exposed rats may be directly related to observed decreases in ATP and phosphocreatine levels and/or to impaired utilization. Moreover, the elevated heart ADP concentrations found in cadmium-fed rats may reflect altered enzyme phosphorylation kinetics in the myocardial cells. It has been postulated that cardiac glycerophosphoryl-choline may act in cation translocation mechanisms or other intracellular processes involving metal ion homeostasis; cadmium forms a stable crystalline complex with this phosphodiester and decreases its level in the heart.

E. Mechanisms in the Reproductive System

1. Testes

While the mechanism of the toxic response of cadmium to the testes is not clearly known, two hypotheses are frequently discussed. One hypothesis states that cadmium causes testicular damage by competing with zinc in zinc-containing enzymes in the testes (Johnson and Walker 1970). A cadmium-sensitive isoenzyme of carbonic anhydrase found in the testes has been reported (Hodgen et al. 1970). Cadmium also appears to interfere with polyamine metabolism (spermine and spermidine) in the rat testes (Furata 1977). The second hypothesis states that cadmium causes vascular changes in the testes leading to ischemia and testicular necrosis (Aoki and Hoffer 1978). It has been reported that hepatic metallothionein does not play an important role in cadmium-induced testicular injury (Wong and Klaassen 1980a). Species and strain differences are important in the susceptibility to cadmium-induced testicular toxicities of interstitial edema, hemorrhage, necrosis and atrophy. Lee and Dixon (1973) suggest cadmium has at least two separate actions on spermatogenic cells: a direct, irreversible interaction with DNA (inhibition of thymidine uptake) and a reversible competitive inhibition of essential zinc metalloenzymes.

2. Fetus

Levin and Adler (1980) reviewed the literature and reported that exposure of pregnant rodents to cadmium has resulted in a variety of fetotoxic effects including growth retardation, anemia, malformations and fetal death. The toxic effects apparently depend on such factors as time and route of administration, dosage, species, strain and nutritional status. Anemia may result from inhibition of resorption of nutrients by unresorbed cadmium in the digestive tract (Sutou et al. 1980a,b). Kelman et al. (1978) found decreased maternal and fetal hematocrits after oral cadmium exposure in rats, also indicating interference with iron metabolism. Gale and Layton (1980) consider cadmium to be a site specific teratogen, i.e., it produces malformations in localized embryonic regions, depending on the time of administration. Since cadmium crosses the placental barrier, the metal acts directly on selected embryonic sites. However, cadmium-induced disturbances in the maternal system or placental tissue may secondarily lead to embryonic damage. Dencker (1975) has suggested that cadmium-induced changes in maternal endocrine function or uterine blood flow are significant factors contributing to fetotoxicity.

Levin and Miller (1980) also suggest maternal toxicity or placental necrosis as factors influencing the fetal toxicity of cadmium. Fetuses directly exposed to cadmium were less adversely affected than those exposed indirectly via maternal exposure. Ferm and Layton (1979) reported that prior cadmium exposure reduces teratogenesis via maternal synthesis of metallothionein.

Ahokas et al. (1980) found reduced fetal zinc content when dams were fed cadmium. They suggested cadmium competitively interacts with placental zinc transfer. This suggestion is supported by the observed depression of zinc-dependent thymidine kinase activity and DNA synthesis in zinc-deficient embryos. Circulating maternal blood zinc concentrations are decreased by maternal cadmium treatment which may also contribute to decreases in fetal zinc in a manner other than direct competition at the placenta. Cadmium-induced fetal growth retardation is a function of reduced cell growth (decreased protein/DNA ratio) and cell division (total DNA). Sutou et al. (1980a) suggested that cadmium-induced disturbances of steroid hormone production in ovaries, placentas and other organs interferes with ovulation and conception, resulting in the observed infertility.

Suzuki et al. (1978) found cadmium inhibited the contractions of isolated guinea pig seminal vesicles normally produced by potassium, calcium, acetylcholine, noradrenaline and barium. They concluded that cadmium inhibits calcium influx and, at high concentrations, calcium release by combining (via SH radicals) with adrenergic and cholinergic receptors resulting in infertility of male rats.

F. Mechanisms in the Immune System

Chronic cadmium exposure can interfere with the functioning of host defense mechanisms in laboratory animals. An increase in sensitivity to bacterial endotoxin and in mortality from bacterial challenge has been described in several rodent species. The inhibition of defense functions in animals treated with cadmium has been attributed to mechanisms involving macrophage dysfunction, impaired bactericidal activity of granulocytes, reduced circulating antibody titer, suppression of antibody synthesis and suppressed responsiveness of lymphocytes to mitogen stimulation (Koller 1973, Koller et al. 1975).

Since most immune defense mechanisms are initiated by the interaction between an antigen and the surface of immunocompetent cells, Kiremidjian-Schumacher et al. (1981a,b) suggested that cadmium may produce its immunotoxicity, at least in part, by altering the surface characteristics of sensitized lymphocytes. They support this contention with their finding that the ionic composition of the cell surface (increased net negative charge) after interaction with antigen in the presence of cadmium was significantly ($P<0.001$) different from the ionic composition after interaction with antigen alone. Such interactions of cadmium with the cell surface may result in activation or inhibition of specific surface receptors, changes in membrane fluidity or interference with the assembly of components of the cytoskeleton involved in cellular motility. Cadmium was also found to interfere with the production of a lymphokine, migration inhibitory factor (MIF), perhaps via the inhibition of cellular oxidative metabolism. However, cadmium interference may also be involved with interactions of the antigen and the cell surface, which is required for initiation of lymphokine synthesis. Cadmium may bind to migration inhibitory factor (a glycoprotein) directly and/or compete with it for sites on the cell surface and, thus, modify or abolish its effect on macrophages. Powell et al. (1979) suggested that cadmium may damage or modify tissue receptors resulting in autoantibody production. Alternatively, they suggest that cadmium may act as a hapten that binds a plasma protein, thus causing antigenic stimulation of the humoral system.

G. Mechanisms for Genetic Effects

Chromosomal aberrations induced by cadmium have been suggested to be an effective biological dosimeter for the mutagenic and carcinogenic potential of cadmium. While the mechanism for genetic effects of cadmium is unknown, calcium is thought to fulfill an essential role in maintaining the structure of chromosomes. In the absence of calcium, other ions may take its place, leading to a perturbation in the DNA-histone bonds and possibly causing chromosome breaks and/or interference with repair processes. Bivalent cations are known to readily bind with different affinities to the nitrogen atoms of the bases and the phosphate groups of DNA. Whereas binding to a phosphate group may stabilize the conformation of DNA owing to neutralization of negative charges, binding to bases, as occurs preferentially with cadmium, can break hydrogen bonds and destabilize the conformation of DNA (Carrabine and Sundaralingan 1971).

Another possible mechanism for heavy metal action (demonstrated for mercury) is the crosslinking of adjacent DNA strands to prevent unwinding and rewinding of DNA. These actions appear to be potentiated in animals on a low calcium diet. Cadmium alters RNA metabolism in several eukaryotic systems. Postulated mechanisms include substitution of cadmium for zinc in RNA polymerases and substitution for calcium which mediates cyclic nucleotide- and protein kinase-dependent regulatory mechanisms (Enger et al. 1979). Jacobson and Turner (1980) have suggested the soft property (chemical species which form their most stable complexes with donor atoms from the second (P, S, Cl) or later period) is the single physicochemical parameter of cadmium and other related divalent cations which correlates with their affinity for nucleic acids and proteins and with toxic effects.

Wallace and Grant (1975) suggested an indirect role of cadmium in prostate cancer via a shift in zinc/hormone balances. Theoretically, cadmium in prostate epithelial cells could bind permanently to thiol groups responsible for the reduction of testosterone to dihydrotestosterone, causing an accumulation of testosterone which could induce or promote cancer. However, accumulation of cadmium in the testes might decrease testosterone, which would presumably have a protective effect. Another possible mechanism is that cadmium accumulation in the pituitary gland causes these changes via altered prolactin and luteinizing hormone production.

H. Synergistic/Antagonistic Effects

Evidence exists which demonstrates that zinc is antagonistic to the toxic actions of cadmium. It has been suggested that part of cadmium's mechanism of toxicity is based upon an exchange with zinc in zinc-dependent enzymes (Friberg et al. 1974). Gunn et al. (1968a,b) reported that zinc acetate (0.30 mmol/kg given in two subcutaneous doses), cysteine (6 mmol/kg, intraperitoneally) and selenium dioxide (0.024 mmol/kg, subcutaneously) each exert protective effects against testicular necrosis induced by cadmium (as $CdCl_2$) (0.012 mM/kg, subcutaneously) in CD-1 mice (30/treatment group). Using ^{109}Cd it was demonstrated that none of the protective agents decreased the amount of cadmium reaching the testis, although cadmium distribution to other organs was somewhat altered. Zinc produced no significant change, cysteine produced a slight increase of the cadmium content, and selenium produced a marked and prolonged elevation of cadmium uptake by the testis (Gunn et al. 1968a). A complete protective effect against testicular injury was exerted by 2,3-dimercaptopropanol (BAL, 0.75 mmol/kg). Since the site of cadmium-induced testicular injury may be in the vasculature, the authors suggest the protective agents exert their action at the vascular level. Although cysteine protects against testicular injury, it enhances lethality of cadmium, lowering the LD_{50} approximately 5-fold. This effect can be explained by the increased renal uptake of cadmium when administered with a variety of thiol compounds. In contrast, methionine and eleven other L-amino acids did not alter the toxicity of cadmium (Gunn et al. 1968b).

Several studies have been undertaken examining the effects of chelating agents such as 2,3-dimercaptopropanol (BAL), hydroxyethylenediaminetriacetic acid (HEDTA), diethylenetriaminepentaacetic acid (DTPA), nitrilotriacetic acid (NTA) and ethylenediaminetetraacetic acid (EDTA) on cadmium tissue distribution (Friberg et al. 1974). Cantilena and Klaassen (1981) tested the effect of several chelating agents (diethyldithiocarbamic acid, DDC; nitrilotriacetic acid, NTA; 2,3-dimercaptopropanol, BAL; DL-penicillamine, PEN; 2,3-dimercaptosuccinic acid, DMSA; ethylenediaminetetraacetic acid, EDTA; diethylenetriamine-pentaacetic acid, DTPA) on the toxicity, excretion, and distribution of cadmium (as $CdCl_2$) in male Swiss Webster mice (age not specified). Various doses of $CdCl_2$ (4 to 10 mg Cd/kg, iv) were administered, followed immediately by an injection of one of the chelators (given ip as a dose equal to one-fourth of the compound's LD_{50}). Survival of the mice was recorded at the end of 14 days. DMSA, EDTA and DTPA, were the most effective in increasing survival. EDTA provided marked protection against cadmium-induced lethality with approximately 80% of the animals surviving at all doses of cadmium tested. DTPA completely protected mice up to 8 mg $CdCl_2$/kg which is two times the intravenous LD_{50} for cadmium. No protective effect was observed with PEN, BAL, or NTA. It should be emphasized that these effects would be significantly different if the chelators were administered at longer intervals after cadmium injection, when the metal is likely to have become largely bound to intracellular metallothionein.

The nutrient composition of the diet can influence the severity of toxic manifestations that occur after a few days or weeks of ingesting high levels of cadmium. Experiments with Japanese quail demonstrated that single deficiencies of zinc, copper, iron and calcium, or combined deficiencies of calcium, zinc and protein intensify the toxic effects of cadmium (Fox et al. 1979). Miller et al. (1974) showed that deficiencies of copper and zinc in a semipurified diet increased alteration of hepatic endoplasmic reticulum in rats exposed to 17.2 mg Cd/L of drinking water. These results suggest that these essential metals may be cadmium antagonists.

Many authors have suggested that the mechanism of cadmium toxicity involves molecular antagonisms between cadmium and essential trace metals, resulting in disruption of cellular homeostatic mechanisms. The hypotheses are consistent with existing experimental evidence that cadmium promotes chronic deterioration of cellular metabolism and ultimately compromises tissue function. This antagonism is potentiated by marginal nutrient deficiences (e.g., calcium, iron, copper, zinc, chromium).

I. Summary

Little is known regarding the biochemical mechanisms by which cadmium causes injury to cells and tissues. Most hypotheses regarding cadmium toxicity which have been proposed fall into one of four categories:

1. Competition of Cd^{2+} with Zn^{2+}. There are numerous zinc-containing enzymes in the body, and Cd^{2+} could interfere in their function by substituting for Zn^{2+} in the enzyme. For example, after cadmium poisoning decreased fetal DNA synthesis might be a result of decreased activity of thymidine kinase, decreased RNA synthesis might be a consequence of decreased activity of RNA polymerase, and injury to testicular cells might be a consequence of decreased activity of carbonic anhydrase. Similar inhibition might be expected for other metalloenzymes.

2. Interaction with Proteins and Enzymes. Cadmium can form complexes with many enzymes or proteins (by binding to either carboxylate or sulfhydryl groups). Formation of such protein-Cd^{2+} complexes could reduce or destroy enzymatic activity. This sort of interaction has been proposed to explain cadmium-induced changes in lymphocyte function (via interactions with cell surface proteins), increased cardiac output (via inhibition of MAO or COMT), decreased spermatogenesis (via inhibition of polyamine synthesis), and decreased hepatic mixed-function oxidase activity (via inhibition of cytochrome P-450).

3. Interaction with DNA. Cadmium can interact directly with chromatin, either with the bases or by cross-linking complimentary strands. Such interactions have been proposed to explain the mutagenic, teratogenic and the cytotoxic effects of cadmium.

4. Competition between Cd^{2+} and Ca^{2+}. Many cell functions depend on normal Ca^{2+} concentrations in extracellular fluid, in intracellular fluid, and in cell membranes. Competition between Ca^{2+} and Cd^{2+} could disrupt these processes and cause a wide variety of dysfunctions. Such a mechanism has been proposed to explain altered activity of cardiac SA nodal cells, and it could underlie other effects as well.

Despite the plausibility of the mechanisms outlined above, little data is available to substantiate these hypotheses. Because so many tissues are affected by cadmium, it is often difficult to distinguish primary from secondary effects. For example, testicular damage may be mediated by a direct effect of cadmium on testicular cells via interaction with DNA or zinc-metalloenzymes, or it may be secondary to an effect of cadmium on the testicular vascular supply, causing vasoconstriction, ischemia and necrosis. Similarly, cadmium-induced osteomalacia could be due to a direct effect on bone cells, but more likely is secondary to altered calcium or phosphate balance resulting from an effect of cadmium on the gastrointestinal tract (altered calcium, phosphate or vitamin D absorption), or on the kidney (altered calcium or phosphate retention, or altered vitamin D activation).

Cadmium toxicity is increased in animals receiving diets deficient in zinc, calcium or protein. Conversely, cadmium toxicity is reduced by feeding zinc, selenium, or cysteine (although cysteine may decrease the LD_{50} for cadmium). A number of chelators also may diminish cadmium toxicity if given shortly after exposure.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Acceptable Daily Intake (ADI) is calculated. From this an Adjusted Acceptable Daily Intake (AADI) and Health Advisory (HA) values for the chemical are then calculated to define the appropriate drinking water concentrations to limit human exposure. For ingestion data, this approach is illustrated as follows:

$$\text{ADI} = \frac{\text{(NOAEL or LOAEL in mg/kg/day)(Body Weight in kg)}}{\text{Uncertainty/Safety Factor}} = \text{mg/day}$$

$$\text{AADI} = \frac{\text{ADI}}{\text{Drinking Water Volume in L/day}} = \text{mg/L}$$

where:

NOAEL = no-observed-adverse-effect level.

LOAEL = lowest-observed-adverse-effect level.

Body weight = 70 kg for adult or 10 kg for child.

Drinking water volume = 2 L per day for adults or 1 L per day for children.

Uncertainty/Safety Factor = 10, 100 or 1,000.

Utilizing these equations, the following drinking water concentrations are developed for non-carcinogenic effects:

1. A one-day HA for 10-kg child.
2. A one-day HA for 70-kg adult.
3. A ten-day HA for 10-kg child.
4. A ten-day HA for 70-kg adult.
5. A lifetime AADI for a 70-kg adult.

The distinctions made between the HA calculations (items 1 through 4) are associated with the duration of anticipated exposure. Items 1 and 2 assume a single acute exposure to the chemical. Items 3 and 4 assume a limited period of exposure (possibly 1 to 2 weeks). The HA values will not be used in establishing a drinking water standard for the chemical. Rather, they will be used as informal scientific guidance to municipalities and other organizations when emergency spills or contamination situations occur. The AADI value (item 5) is intended to provide the scientific basis for establishing a drinking water standard based upon non-carcinogenic effects.

A NOAEL or LOAEL is determined from animal toxicity data or human effects data. For animal data, this level is divided by an uncertainty factor because there is no universally acceptable quantitative method to extrapolate from animals to humans. The possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human data, an uncertainty factor is also used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxic chemicals. An Office of Drinking Water (ODW) modification of the guidelines set forth by the National Academy of Sciences (NAS 1977, 1980) is typically used in establishing uncertainty factors as follows:

- An uncertainty factor of 10 is used when good acute or chronic human exposure data identifying a NOEL/NOAEL are available and are supported by acute or chronic toxicity data in other species.

- An uncertainty factor of 100 is used either when good acute or chronic toxicity data identifying NOEL/NOAEL are available for one or more animal species (but human data are not available), or when good acute or chronic toxicity data identifying a LOAEL in humans are available.

- An uncertainty factor of 1,000 is used either when limited or incomplete acute or chronic toxicity data are available, or when good acute or chronic toxicity data identify a LOAEL (but not a NOEL/NOAEL) for one or more animal species.

The uncertainty factor used for a specific risk assessment is judgmental. Factors that cannot be incorporated in the NAS/ODW guidelines for selection of an uncertainty factor, but must be considered include: (1) the quality of the toxicology data, (2) the significance of the adverse effect and (3) the existence of counterbalancing beneficial effects.

If toxicological evidence requires the chemical to be classified as a potential carcinogen (there is insufficient evidence to classify cadmium as a carcinogen following oral exposure), mathematical models are used to calculate the estimated excess cancer risks associated with the ingestion of the chemical via drinking water. The bioassay data used in these estimates are from animal experiments. In order to predict the risk for humans from these data, it must be converted to an equivalent human dose. This conversion includes correction for non-continuous animal feeding, non-lifetime studies and for the difference in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average human body weight is 70 kg and that the average human consumes 2 liters of water per day. The multistage model is then fit to the equivalent human data to estimate the risk at low doses. The upper 95% confidence limit of this estimate is used. Excess cancer risks can also be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. There is no basis in the current understanding of the biological mechanisms involved in cancer to choose among these models. The estimates of low doses for these models can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of risk rate levels has an inherent uncertainty. This is because the tools of scientific measurement, by their very nature, involve both systematic and random error. In most cases, only studies using experimental animals have been performed. There is thus uncertainty when the data are extrapolated to humans. When developing risk rate levels, several other areas of uncertainty exist, such as (1) incomplete knowledge concerning the health effects of contaminants in drinking water, (2) the impact of test animal age, sex and species and the nature of target organ systems examined on the toxicity study results and (3) the actual rate of exposure of internal targets in test animals or humans. Dose-response data are usually only available for high levels of exposure, not for the lower levels of exposure for which a standard is being set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

A. Non-Carcinogenic Effects

Cadmium is a biologically non-essential element which has been detected as a contaminant of food, water and air. Studies in animals and humans have demonstrated that cadmium is not rapidly absorbed from the gastrointestinal tract. Friberg et al. (1974) and Shaikh and Smith (1980) reported values of 3% to 5% for gastrointestinal absorption. However, cadmium is excreted from the body so slowly that it accumulates in body tissues following acute or chronic exposures (see Section III.B., III.D. and III.E). The toxic effects associated with cadmium exposure are dependent on the magnitude, route and duration of exposure.

Tsuchiya (1969a,b) and Murata et al. (1970) described the disease Itai-Itai, prevalent in adult inhabitants of cadmium-polluted areas of Japan. The prominent signs and symptoms of Itai-Itai disease include osteomalacia, osteoporosis, bone pain, increased fractures, proteinuria, glucosuria and anemia. Epidemiological evidence associates chronic cadmium ingestion with Itai-Itai disease.

1. Short-Term Exposure

Most short-term evaluations of cadmium toxicity in animals focus on estimating LD_{50} values following oral ingestion. The LD_{50} values vary from 5 to more than 5,000 mg Cd/kg, depending on animal species, sex and age and the chemical form of cadmium evaluated. For example, estimates of the LD_{50} for $CdCl_2$ in the rat range from 88 to 302 mg/kg, and the LD_{50} for cadmium acetate is 333 mg/kg. However, lethality data are inadequate for derivation of one-day and ten-day Health Advisories.

Kotsonis and Klaassen (1978) studied the effects of cadmium ingestion on a number of biological parameters in rats. Male Sprague-Dawley rats (initially 50- to 70-days-old) were supplied drinking water containing 0, 10, 30 or 100 mg Cd/L (as $CdCl_2$) for 24 weeks. There were six to nine animals in each exposure group. The mean daily water intake was 0.042, 0.041, 0.036 and 0.028 L/day; the mean final body weight was 0.486, 0.488, 0.506 and 0.438 kg; and the mean daily dose was approximately 0, 0.84, 2.15 and 6.44 mg Cd/kg/day for each exposure group, respectively. Rats receiving water containing 30 or 100 mg Cd/L (2.15 or 6.44 mg Cd/kg/day), developed significant ($P<0.05$) proteinuria after six weeks of exposure. Rats rats receiving water containing 10 mg Cd/L (0.84 mg Cd/kg/day) developed no significant ($P>0.05$) proteinuria during the 24-week study.

Case studies of acute oral cadmium poisoning in humans have implicated ingestion of food or liquid contaminated during storage in cadmium-plated containers as the cause of gastrointestinal symptoms. Acute effects were observed following ingestion of contaminated coffee (800 mg Cd/L), wine (126 mg Cd/L), punch (67 mg Cd/L) and water (0.5 to 16 mg Cd/L) (CEC 1978, Frant and Kleeman 1941, Carstensen and Poulsen 1973). Initial symptoms included nausea, vomiting, diarrhea, muscle cramps and salivation (Arena 1963). Severe poisoning results in liver injury, convulsions, renal failure, cardiopulmonary depression and shock. Death may occur in 1 to 14 days (CEC 1978).

The threshold for an emetic effect (nausea and vomiting) in humans was estimated to be a dose of 3 mg Cd (0.043 mg/kg for 70-kg adult) (CEC 1978). Lauwerys (1979) also estimated the NOAEL for a single oral dose to be 3 mg Cd. Friberg et al. (1979) reported that ingestion of water containing 15 mg Cd/L could induce the emetic response in humans. Assuming that eight ounces of water were ingested, the dose for the emetic effect was calculated to be 3.6 mg (15 mg Cd/L x 0.240 L = 3.6 mg). Thus, the dose-estimate based on the 15 mg/L concentration reported by Friberg et al. (1979) is also consistent with the 3 mg threshold dose for the emetic effect reported by CEC (1978) and the NOAEL reported by Lauwerys (1979).

2. Long-Term Exposure

The effects of chronic exposure to cadmium have been extensively evaluated in animals and humans. Decker et al. (1958) exposed groups of 34-day-old albino Sprague-Dawley rats to drinking water containing cadmium (as $CdCl_2$) at concentrations of 0, 0.1, 0.5, 2.5, 5.0, 10.0 or 50.0 mg Cd/L (approximately 0, 0.008, 0.035, 0.181, 0.361, 0.735 or 3.04 mg Cd/kg/day, based on mean final body weights of 0.413, 0.359, 0.433, 0.414, 0.415, 0.408 and 0.230 kg and mean reported water consumption of 0.030 L/day for all groups except the 50 mg/L group which consumed only 0.014 L/day). Each exposure group included eight male and eight female rats and the control group included ten rats of each sex. For the rats exposed to 0.1 to 10 mg Cd/L (0.008 to 0.735 mg Cd/kg/day) for 12 months, no adverse effects were observed in general health, growth rate or blood chemistry, and examinations for pathological changes were negative. Rats that were exposed to water containing 50.0 mg Cd/L for three months developed anemia and did not gain weight normally. The authors reported that all groups had mortality due to a respiratory infection but there was no evidence that cadmium exposure influenced the prevalence of the infection. From this study, 0.735 mg Cd/kg/day represents the NOAEL in rats.

There have been several experimental studies that suggest that cadmium may be a causative agent in hypertension. The role of cadmium exposure in experimental and human "essential" hypertension remains a matter of controversy and conjecture.

Perry et al. (1977a) evaluated the effect of chronic (up to 30 months) cadmium ingestion on systolic blood pressure in rats. Groups of 16 female Long-Evans rats were exposed to drinking water containing cadmium (as cadmium acetate) at concentrations of 1, 2.5, 5, 10, 25 or 50 mg Cd/L (approximately 0.075, 0.188, 0.375, 0.750, 1.667 or 5.00 mg Cd/kg/day based on assumed final body weights of 0.400 kg (for 1, 2.5, 5 and 10 mg/L groups), 0.375 kg (for 25 mg/L group) and 0.250 (for 50 mg/L group) and reported daily water consumptions of 0.030 L (for 1, 2.5, 5 and 10 mg/L groups) and 0.025 L (for 25 and 50 mg/L groups)). The control group (64 female rats) received no cadmium via drinking water. The drinking water for all groups was fortified with essential trace metals (10 mg Mn/L, 1 mg Co/L, 5 mg Cu/L, 50 mg Zn/L and 1 mg Mo/L). The animals were housed in a low-contamination environment and fed a rye-based low-cadmium diet. Systolic blood pressure was measured in triplicate at six-month intervals by the tail cuff (indirect) method. The rats were lightly anesthetized (35 mg/kg of sodium pentobarbital, ip) prior to blood pressure measurements. Groups of rats exposed to 1, 2.5, 5, 10 or 25 mg Cd/L had significantly ($P<0.01$) elevated mean systolic blood pressure (relative to controls) at one or more of the (6, 12 or 18 month) observation intervals. A significant elevation of mean systolic blood pressure was consistently observed at the 6-, 12-, 18-, 24- and 30-month observation intervals for groups exposed to 2.5 and 5 mg Cd/L. Therefore, hypertension was observed at all dose levels evaluated and the best estimate of a LOAEL in rats from this study is 0.075 mg Cd/kg/day (1 mg Cd/L in drinking water).

Perry et al. (1977b) described additional studies of blood pressure responses in rats chronically exposed to drinking water containing low concentrations of cadmium. Experimental methods similar to those described in Perry et al. (1977a) were used. Groups of 20 female Long-Evans rats were exposed for 15 or 18 months to drinking water containing cadmium (as cadmium acetate) at 0.01, 0.03, 0.10, 0.25, 0.50 or 5.0 mg Cd/L (0.001, 0.003, 0.009, 0.023, 0.047, 0.467 mg Cd/kg/day, assuming body weight of 0.290 and water consumption of 0.027 L/day). The drinking water was also supplemented with trace essential metals. The two control groups contained 60 and 40 rats.

Systolic blood pressure was measured as previously described, with the exception that the animals were anesthetized with 25 mg/kg of sodium pentobarbital. Significant ($P<0.05$) increases in systolic blood pressure (10 to 24 mm Hg above control) were observed in animals exposed to 0.1, 0.25, 0.5 and 5 mg Cd/L for 6 to 18 months. There were no other signs of toxicity. Thus, the LOAEL for hypertension based on the 0.1 mg Cd/L exposure was 0.009 mg Cd/kg/day. The groups exposed to 0.01 or 0.03 mg Cd/L had average systolic blood pressures that were not significantly elevated above the controls at the end of 15 months. Thus, the NOAEL for hypertension based on the 0.03 mg Cd/L exposure is 0.003 mg Cd/kg/day. Perry et al. (1979) also reported data that support the LOAEL and NOAEL for hypertension identified above.

Kopp et al. (1982) summarized results of collaborative studies with Perry on the effects of cadmium in weanling female Long-Evans rats. The animals (520 total) were housed in a low-contamination environment and fed (ad lib.) a rye-based low-cadmium diet and deionized water fortified with essential trace metals. Nine concentrations of cadmium (as cadmium acetate) from 0.01 to 50.0 mg Cd/L (approximately 0.0007 to 3.45 mg Cd/kg/day, assuming drinking water consumption of 0.020 L/day and body weights of 0.290 kg) were administered via drinking water. Each exposure group contained at least 16 animals, and the control population contained a comparable number of rats. Following 18 months of exposure to 0.5 mg Cd/L (approximately 0.03 mg Cd/kg/day), systolic blood pressure was elevated by 20%. This group (approximately 0.03 mg Cd/kg/day) demonstrated the maximum blood pressure response. Exposures to higher and lower cadmium concentrations produced less pronounced elevation of systolic blood pressure. Exposure to concentrations greater than 10 mg Cd/L (approximately 0.69 mg Cd/kg/day) caused depressor responses (approximately 4 to 12 mm Hg). The graphical presentation of systolic blood pressure change versus log cadmium concentration in drinking water reported by Kopp et al. (1982) indicated only minor elevations (2 to 4 mm Hg) of blood pressure for the 0.01 and 0.03 mg Cd/L (0.001 and 0.002 mg Cd/kg/day, respectively) exposure groups. However, the statistical significance of the observed systolic blood pressure changes was not reported.

Kopp et al. (1983) continued these studies in rats supplied with drinking water that contained 1 mg Cd/L (approximately 0.062 mg Cd/kg/day, assuming water consumption of 0.030 L/day and reported body weight of 0.483 kg). Again, no overt toxicity (decreased growth rate, etc.) was observed, but a persistent, mild hypertension was evident after two months. These data support the hypothesis that cadmium may contribute to hypertension.

Chronic cadmium exposure has also been implicated as a risk factor in human "essential" hypertension. Schroeder (1965) studied relationships between renal cadmium concentrations and causes of mortality among 187 adults from the continental U.S. and 171 adults from other nations. The mean renal cadmium concentration in uses where mortality was due to hypertensive disease was significantly ($P<0.05$) higher than that in cases where mortality was due to accidents or arteriosclerotic disease (see Table VI-7 for details). Unfortunately, retrospective epidemiological studies such as this are complicated by the inability to correct and account for other variables associated with hypertension. Thus, these data are not sufficient to establish a causal relationship.

The kidney is proposed to be the critical (most sensitive) target organ in humans chronically exposed to cadmium by ingestion (CEC 1978). The early clinical signs of renal injury include proteinuria, glucosuria and aminoaciduria. The critical concentration of cadmium in the renal cortex that induces renal dysfunction (i.e., proteinuria) has not been unequivocally or precisely determined.

Based on a comprehensive literature review, Friberg et al. (1974) concluded that renal damage may occur when the cadmium concentration in the renal cortex of humans exceeds 200 µg/g wet weight. The authors stated that:

> "Evidence from animal experiments and from analyses of cadmium in kidneys from workers exposed to cadmium indicates that renal dysfunction may become manifest at levels around 200 µg/g wet weight in renal cortex.... It is considered justified to start out from a value of 200 µg/g cadmium in renal cortex (wet weight) when discussing which exposures can bring about cadmium-induced detectable renal dysfunction in man. This, of course, does not mean that 200 µg/g would give rise to renal tubular dysfunction in all persons exposed."

The 200 µg/g value is probably the most widely accepted estimate of the critical concentration for renal dysfunction (NAS 1977, CEC 1978). Estimates of the critical concentration in the human renal cortex range from 50 µg/g (Brown et al. 1978) to 300 µg/g (Nomiyama 1977). Roels et al. (1983) reevaluated their previous estimate of 160 µg/g and reported that the critical concentration in the human renal cortex is 216 µg/g. This was based on in vivo determination of renal cadmium (by neutron capture γ-ray analysis) in 309 male workers at zinc-cadmium plants and determination of kidney function by β_2-microglobulin, total protein, and albumin urinalysis. Recently Kjellstrom et al. (1984) pointed out that different groups employed different functional or conceptual criteria to identify the critical concentration. These authors propose that the term "population critical constant" (PCC) should be used instead of "critical concentration" when assessing population based data. The PCC would be calculated for a particular response rate in the population (e.g., 10%), and this would be written as PCC-10 (analogous to the concept of LD-50). Employing this definition, and using improved data regarding the ratio of kidney cortex to total kidney mass (1/1.25 versus 1/1.50), the authors concluded that the PCC-10 for human renal cortex was 180 to 220 μg/g.

In normal humans from the U.S. and Sweden not exposed to elevated levels of cadmium, renal cortical concentrations increase with age and reach a peak of about 50 μg/g tissue by age 50 (Friberg et al. 1974, Schroeder and Balassa 1961, Schroeder et al. 1967). WHO (1972) also reported that cadmium concentrations in the renal cortex range from 25 to 50 μg/g tissue wet weight for adult subjects from the U.S. The NAS (1977) reported "limited autopsy data suggest that the renal cortical concentrations of cadmium in American and European populations are generally less than 50 μg/g of tissue (wet weight)...." The renal cortical concentration occurring in the U.S. population (i.e., less than 50 μg/g) is "less than the projected critical concentration by a factor of four or more" (NAS 1977).

Friberg et al. (1974) estimate that a cadmium intake of 352 μg/day for 50 years is required to accumulate 200 μg Cd/g tissue in the renal cortex of humans. This assumes a daily excretion rate of 0.01% total body burden and a daily absorption of 4.5% (see Table VIII-1). Thus, the estimated daily cadmium intake producing the critical concentration in the human renal cortex after 50 years of exposure is estimated to be 0.352 mg/day.

Table VIII-1 Daily Cadmium Excretion and Corresponding Cadmium Intake for Adult Humans[a]

Daily cadmium excretion (% of body burden)[b,c]	Cd intake (μg/day) required to accumulate 50 μg Cd/g renal cortex[d]	Cd intake (μg/day) required to accumulate 200 μg Cd/g renal cortex[d]
0	41	164
0.002	--	196
0.005	62	248
0.01	88	352
0.02	154	616
0.05	384	--

[a] Based upon amount of intake required to accumulate 50 μg Cd/g and 200 μg/g renal cortex by age of 50.

[b] Assuming 4.5% gastrointestinal tract absorption.

[c] Assuming 33% of body burden is in kidney.

[d] Assuming that renal cortex cadmium concentration is 150% of that in the average whole kidney. Assuming daily caloric intakes varies with age. Based upon adults consuming 2,500 cal/day.

Adapted from Friberg et al. (1974).

B. Quantification of Non-Carcinogenic Effects

1. One-Day Health Advisory

The NOAEL (for gastrointestinal irritation) of 3 mg as a single oral dose to adult humans (0.043 mg/kg for a 70-kg adult) (Lauwerys 1979) has been selected to serve as the basis for the 10-kg child one-day HA. More suitable data are not available for making this calculation. Assumptions regarding absorption are not required in the calculation since the emetic effect is most likely a direct and reversible action on the gastrointestinal mucosa.

The one-day HA for the 10-kg child is calculated as follows:

One-Day Health Advisory for Child:

$$\frac{(0.043\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})\ (10)} = 0.043\ \text{mg/L}\ (43\ \mu\text{g/L})$$

where:

0.043 mg/kg/day = NOAEL for emetic effects following acute exposure in adult humans (Lauwerys 1979).

10 kg = assumed weight of child.

1 L/day = assumed water consumption by a 10-kg child.

10 = uncertainty factor. This uncertainty factor was selected based upon the NAS/ODW guidelines in which a NOAEL from human exposure data is used.

The one-day HA for the 70-kg adult is calculated as follows:

One-Day Health Advisory for Adult:

$$\frac{(0.043\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})\ (10)} = 0.15\ \text{mg/L}\ (150\ \mu\text{g/L})$$

where:

0.043 mg/kg/day = NOAEL for emetic effects following acute exposure in adult humans (Lauwerys 1979).

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by a 70-kg adult.

10 = uncertainty factor. This uncertainty factor was selected based upon the NAS/ODW guidelines in which a NOAEL from human exposure data is used.

The National Academy of Science (NAS 1982) established a Suggested No-Adverse-Response Level (SNARL) of 0.150 mg Cd/L for a 24-hour exposure to a 70-kg adult human. This was based on the threshold emetic dose for humans of approximately 3 mg cadmium supported by studies cited in Arena (1963). A daily water consumption of two liters and a safety factor of ten were used to establish the 24-hour SNARL.

2. Ten-Day Health Advisory

No appropriate studies following short-term, repeated oral exposures (up to 14 days) to cadmium were located in the available literature. Consequently the study by Kotsonis and Klaassen (1978) has been selected to serve as the basis for calculation of the 10-day HA. This was a 24-week study that demonstrated that rats receiving water containing 10 mg Cd/L (0.84 mg

Cd/kg/day) did not develop significant ($P>0.05$) proteinuria, while rats receiving 30 or 100 mg Cd/L (2.15 or 6.44 mg Cd/kg/day) did develop proteinuria after 6 weeks. Thus, 10 mg Cd/L (approximately 0.84 mg Cd/kg/day) represents the NOAEL. Consideration of gastrointestinal absorption is not required in the HA calculations, because the NOAEL is based upon an intake dose rather than an absorbed dose. However, it should be noted that animal studies have shown that absorption is age and sex dependent (Sasser and Jarboe 1977, Kostial et al. 1979, 1983). Whether absorption in humans is also age and sex dependent is unknown.

The ten-day HA for the 10-kg child is calculated as follows:

Ten-Day Health Advisory for Child:

$$\frac{(0.84 \text{ mg/kg/day})\ (10 \text{ kg})}{(1 \text{ L/day})\ (1{,}000)} = 0.008 \text{ mg/L } (8\ \mu\text{g/L})$$

where:

0.84 mg/kg/day = NOAEL for proteinuria following up to 24-weeks of cadmium oral exposure in rats (Kotsonis and Klaassen 1978).

10 kg = assumed weight of child.

1 L/day = assumed water consumption by a 10-kg child.

1,000 = uncertainty factor. This uncertainty factor was selected based upon the NAS/ODW guidelines when using a NOAEL derived from an animal study conducted in one species with only six animals per dose group.

The ten-day HA for the 70-kg adult is calculated as follows:

Ten-Day Health Advisory for Adult:

$$\frac{(0.84\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})\ (1{,}000)} = 0.029\ \text{mg/L}\ (29\ \mu\text{g/L})$$

where:

0.84 mg/kg/day = NOAEL for proteinuria following up to 24-weeks of cadmium oral exposure in rats (Kotsonis and Klaassen 1979).

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by a 70-kg adult.

1,000 = uncertainty factor. This uncertainty factor was selected based upon the NAS/ODW guidelines when using a NOAEL derived from an animal study conducted in one species with only six animals per dose group.

The National Academy of Science (NAS 1982) established a Suggested No-Adverse-Response Level (SNARL) of 0.021 mg Cd/L for a seven-day exposure to a 70-kg adult human. This was calculated by dividing the 24-hour SNARL (based on the threshold emetic dose for humans reported by Arena 1963) by a factor of seven. The NAS also calculated a SNARL for a seven-day exposure on the basis of the "provisional tolerable weekly intake" of 6.7 to 8.3 µg Cd/kg body weight for humans reported by Benes (1978) and WHO (1973). The alternative seven-day SNARLs of 0.0235 mg/L and 0.029 mg/L were calculated for the respective endpoints of the range of tolerable intakes, assuming a safety factor of 10 and 100% of total cadmium intake by a 70-kg adult human was from drinking water. All of the NAS seven-day SNARL values compare favorably with the ten-day HA value for the adult calculated here.

3. Adjusted Acceptable Daily Intake

There are no adequate oral exposure studies in humans which provide a NOAEL for the chronic effects of cadmium. Friberg et al. (1974) concluded that the critical concentration of cadmium in the renal cortex of humans associated with renal dysfunction is 200 µg/g wet weight, and this is supported by the recent reassessment by Kjellstrom et al. (1984). The 200 µg/g critical concentration was based on a comprehensive review of evidence from animal experiments and from analyses of kidneys from workers occupationally exposed to cadmium. The 200 µg/g value is probably the most widely accepted estimate of the critical concentration for renal dysfunction (CEC 1978, NAS 1977). Roels et al. (1983) reported that the critical concentration in the human renal cortex is 216 µg/g tissue wet weight and that less than 10% of occupationally exposed males may develop renal dysfunction at this concentration.

Several models have been proposed to estimate the daily intake (exposure) of cadmium required to produce the critical concentration in the renal cortex. Each model has inherent limitations. Friberg et al. (1974) estimated that a daily intake of 0.352 mg Cd/day for 50 years would result in a renal cortex concentration of 200 µg Cd/g. This model assumes 4.5% absorption of the daily oral dose and 0.01% excretion per day of the total body burden. The absorption and excretion rates used by Friberg et al. (1974) are reasonable estimates (see Section III). Thus, 0.352 mg Cd/day is a reasonable estimate of the daily intake required to produce the critical concentration for renal dysfunction in a 70-kg adult human. This estimated intake was selected as the basis for the AADI calculation. Alternative oral dose levels associated with other absorption and excretion rates are summarized in Table VIII-1.

The ADI for a 70-kg adult is calculated as follows:

ADI:

$$\frac{(0.352 \text{ mg/day})}{(10)} = 0.035 \text{ mg/day } (35\ \mu\text{g/day})$$

where:

0.352 mg/day = estimated human daily cadmium intake resulting in a renal cortical concentration of 200 μg/g wet weight (critical concentration for renal dysfunction) at age 50 in human adult (Friberg et al. 1974).

10 = uncertainty factor. This uncertainty factor was selected based on the NAS/ODW guidelines to include consideration of using human data supported by toxicity data from other species. Also, the uncertainty factor takes into consideration the reasonable absorption and excretion rates used to estimate the daily intake.

Using 0.035 mg/day as the ADI and assuming the 70-kg adult consumes two liters of drinking water per day, the AADI is calculated as follows:

AADI:

$$\frac{0.035 \text{ mg/day}}{2 \text{ L/day}} = 0.018 \text{ mg/L } (18 \text{ µg/L})$$

This AADI calculation assumes 100% of the human exposure derives from drinking water. This value may be modified upon the availability of relative source contribution data which provide estimates of human exposure from food, air and possibly the occupational environment. It is recognized that the 10-day HA value for the child is lower than this AADI value. This will be considered during the process of deriving guidelines and standards for cadmium in drinking water.

While calculation of the ADI based upon human data emphasizing renal damage currently appears to be most appropriate, Perry et al. (1977b, 1979), Kopp et al. (1982) and others have shown a reproducible increase in systolic blood pressure in rats administered cadmium in drinking water in doses as low as 0.1 mg Cd/L (approximately 0.009 mg Cd/kg/day). No significant increase in systolic blood pressure was observed in rats receiving water containing 0.01 or 0.03 mg Cd/L (0.001 and 0.003 mg Cd/kg/day, respectively) for 15 months (Perry et al. 1977b). If it were decided to use hypertension (rather than renal damage) as the most appropriate index of cadmium toxicity, the data above suggest the NOAEL is about 3 µg/kg/day. For a 70-kg adult, this corresponds to 210 µg/day, but division by the uncertainty factor of 100 which is appropriate for use of animal data yields an ADI of only 2 µg/day. Assuming a 70-kg adult consumes 2 L of water per day, this corresponds to an AADI of 1 µg/L. It does not seem prudent or practical to establish such a very low AADI value at this time, but the importance of further research into the role of cadmium in human hypertension is evident.

The National Academy of Science (NAS 1982) established a Suggested No-Adverse-Response Level (SNARL) of 0.005 mg/L for chronic exposure to a 70-kg adult human. The SNARL was based on the study by Decker et al. (1958) who observed no effects in rats exposed to 10 mg Cd/L (approximately 0.75 mg Cd/kg/day based on a daily drinking water consumption of 0.030 L and body weight of 0.400 kg assumed by NAS) for one year. The NAS calculated the SNARL using a safety factor of 1,000 and an assumed 20% exposure from drinking water for a 70-kg adult human consuming 2 L/day of drinking water.

The maximum contaminant level (MCL) for cadmium in drinking water (0.010 mg Cd/L) was also based on the estimated human daily intake of 352 μg Cd resulting in a renal cortical concentration (associated with proteinuria) of 200 μg/g wet weight at age 50 (USEPA 1976). The estimated daily intake to produce the critical concentration in human renal cortex at age 50 was calculated assuming 5% gastrointestinal absorption, rapid excretion of 10% of absorbed dose and 0.05% daily excretion of the total body burden. The EPA noted that ingestion of two liters of drinking water with a cadmium concentration at the MCL (0.010 mg/L) contributes 20 μg/day to the assumed dietary intake of 75 μg/day. Thus, the EPA estimated drinking water to contribute approximately 20% of the total oral cadmium intake (95 μg/day). The total oral intake from food and drinking water (95 μg/day) provided a safety factor of approximately four-fold below the intake estimated to produce proteinuria (352 μg/day). The EPA did not take into account cadmium exposure from cigarette smoke.

C. Carcinogenic Effects

Cadmium and cadmium compounds have been shown to induce sarcomas at injection sites in animals when administered parenterally (Haddow et al. 1964, Gunn et al. 1967) and cadmium chloride administered by aerosol for 18 months can produce lung tumors in rats (Takenaka et al. 1983). However, feeding studies have never demonstrated an association between an increased incidence of tumors or any specific type of neoplasia and oral cadmium ingestion (Schroeder et al. 1965, Kanisawa and Schroeder 1969a, Loser 1980). Evidence regarding carcinogenicity of cadmium in humans following oral exposure is largely conjectural. The U.S. EPA (USEPA 1980) has recommended that cadmium not be considered a suspect human carcinogen for the purpose of calculating an ambient water quality standard.

Although there are conflicting reports, cadmium is considered to be weakly mutagenic (see Section V; USEPA 1983). The mutagenic effects reported depend, in part, on the test system used for analysis (USEPA 1983). Cadmium has been shown to be teratogenic in animals (see Section V; Schroeder and Mitchener 1971), although when cadmium is administered to pregnant female mice in drinking water, cadmium accumulates in the placenta and very little transfers to the fetus (Bhattacharyya et al. 1982). When administered parenterally, cadmium induces an acute testicular necrosis (Parizek 1957), but apparently little damage occurs at low chronic doses (Kotsonis and Klaassen 1978).

D. Quantification of Carcinogenic Effects

The International Agency for Research on Cancer (IARC) has performed an assessment of the degree of evidence for the carcinogenicity of cadmium to humans and in experimental animals (WHO 1982). This assessment concluded that cadmium is a Group 2B chemical (a relatively low degree of evidence exists to demonstrate that the chemical is probably carcinogenic to humans).

No risk assessments on the carcinogenic risk of orally ingested cadmium have been calculated by the International Agency for Research on Cancer (IARC 1976) or the National Academy of Science (NAS 1982). The Carcinogen Assessment Group (CAG) (USEPA 1983) has calculated a lifetime risk from atmospheric cadmium based upon evidence that suggests inhaled cadmium may induce respiratory and prostate cancers in humans. The CAG (USEPA 1983) estimated that the upper-bound cancer risk from lifetime exposures to 1 µg Cd/m^3 ranges from 1.9×10^{-3} to 2.5×10^{-3}. This risk estimate is based on the Lemen et al. (1976) epidemiological study of prostate and lung cancer rates of cadmium smelter workers. The CAG (USEPA 1983) also calculated 0.15 as the upper-bound cancer risk for humans with lifetime exposure to 1 µg/m^3 on the basis of rat experimental data. This was based on the Takenaka et al. (1983) study of lung carcinomas in rats with lifetime inhalation exposures to cadmium chloride aerosols. The CAG (USEPA 1983) concluded that further analysis and research is required to resolve the 100-fold difference between cancer risk estimates based on human versus animal data. The role of cadmium in the induction of cancer remains largely a matter of controversy and conjecture. Therefore, it is inappropriate to derive any carcinogenic risk values for cadmium in drinking water at this time.

E. Existing Guidelines and Standards

The World Health Organization (WHO 1983) has recommended that cadmium concentrations not exceed 0.005 mg/L in drinking water. The Commission of the European Communities (CEC 1975) has proposed the same standard and later (CEC 1978) suggested that the threshold effect corresponds to ingestion of a total (from all sources) of 200 to 248 μg daily for the non-smoker and 169 μg daily for the cigarette smoker. A FAO/WHO expert committee proposed a provisional tolerable weekly intake of no more than 400 to 500 μg (57.1 to 71.4 μg/day) (WHO 1972). The current U.S. EPA drinking water standard is 0.010 mg/L (USEPA 1976). The National Academy of Sciences has calculated Suggested No-Adverse-Response Levels (SNARLs) for a chronic exposure (0.005 mg/L), 7-day exposure (0.021 mg/L) and 24-hour exposure (0.150 mg/L) (NAS 1982).

The recommended threshold limit values (TLV) for cadmium dusts, salts and oxide fumes for occupational eight hour time-weighted average exposure is 0.05 mg/m^3 (ACGIH 1980).

F. Special Considerations

1. High Risk Populations

Factors such as diet, age, sex and individual and genetic variation appear to influence susceptibility to cadmium toxicity. Investigators have shown that the nutrient composition of the animal diet markedly influences the severity of toxic manifestations that occur after administration of high levels of cadmium for a few days or weeks (Table VIII-2). The animal data suggest that humans with dietary deficiencies of calcium, protein, zinc, iron or copper may be at greater risk due to increased cadmium absorption and toxicity. Thus, populations with abnormal nutritional status may potentially be at higher risk.

Cadmium accumulates in the body with age, especially in the kidney and liver. This increase is approximately linear within the age interval of 5 to 50 years with a slight decrease occurring after 50 to 60 years of age. Studies have shown that young age groups might be at special risk because of a greater gastrointestinal absorption and gut retention rates than those observed in adults (Kostial et al. 1979, 1983). However, no clinical or epidemiological evidence exists to demonstrate that children, as a group, are more sensitive or at greater risk to the adverse health effects of cadmium.

Results from the study of cadmium pollution in Japan indicate that women are more susceptible to Itai-Itai disease (a painful disease of the bones) than men. Multiparous women (i.e., post-menopausal with several deliveries) seemed at highest risk. Increased susceptibility of female experimental animals to the adverse effects of cadmium has also been observed. Pregnant women may be a special group at increased risk due to the potential effects of cadmium on the fetus. Ohanian et al. (1978a) demonstrated that the genetic background of animals plays an important role in cadmium-induced hypertension and its complications. It is not known whether there are significant racial or ethnic differences in human sensitivity to cadmium.

Table VIII-2 Relationships Between Cadmium and Essential Nutrients

Nutrient	Dietary intake of individual nutrients: Normal[a]	Deficiency[b]	Excess[c]
Zinc	+	+	+
Iron	+	+	+ (Fe^{2+})
Manganese	+	?[d]	?
Copper	+	+	+
Selenium	+	?	+
Calcium	+	+	?
Ascorbic acid	?	?	+
Vitamin D	?	+	?
Protein	?	+	+

[a] + = Cadmium affects metabolism and/or function of the nutrient.

[b] + = A deficiency of the nutrient increases the severity of cadmium toxicity.

[c] + = An excess of the nutrient decreases the toxicity of cadmium.

[d] ? = No relationship has been established.

Adapted from Fox (1974).

Due to the cadmium content of tobacco, cigarette smokers represent a population at higher risk to cadmium exposure and toxicity. Hammer et al. (1973) compared the cadmium content of various tissues in 40 to 70 year-old males who were either non-smokers or smokers (one-half pack per day or more). The cadmium burdens in kidney, liver and whole body were increased by over two-fold in the smokers. Similar results have been obtained by Lewis et al. (1972) who found a doubling of the cadmium content in liver, kidney and lung in smokers (one pack per day for 40 years) compared to non-smokers. Thus, cigarette smokers are likely to have a higher body burden of cadmium and a decreased margin-of-safety compared to non-smokers.

2. Interactions

The synergistic, antagonistic or additive interactions between minerals, trace essential metals, non-essential metals, amino acids or vitamins and cadmium are complex and not thoroughly understood. Zinc, selenium and cysteine each exerted a protective effect against testicular necrosis induced in mice by administration of cadmium (Gunn et al. 1968a,b). Cysteine protected against testicular necrosis but enhanced lethality of cadmium (i.e., approximately a five-fold decrease in the LD_{50}). Single deficiencies of zinc, copper, iron and calcium or combined deficiencies of calcium, zinc and protein intensified cadmium toxicity in Japanese Quail (Fox et al. 1979). Deficiencies of copper, iron and zinc have been found to increase cadmium uptake and toxicity (Banis et al. 1969, Bunn and Matrone 1966, Miller et al. 1974), although no effect of zinc deficiency was observed by Hahn and Evans (1975) or Foulkes and Voner (1981). These results suggest that the amino acids, essential metals and minerals may be cadmium antagonists.

Intraperitoneal administration of chelators (EDTA, DMSA or DTPA) reduced mortality among mice administered lethal doses of cadmium (intravenously), provided the chelators were given immediately after the cadmium. However, other chelators (PEN, BAL and NTA) provided no protective effect against lethality (Cantilena and Klaassen 1981).

There is a paucity of data demonstrating interactions of cadmium with food, xenobiotics and essential or non-essential metals. However, marginal dietary deficiencies may affect antagonistic interactions that decrease cadmium toxicity.

3. Other Factors

The derivation of the AADI is based on the critical concentration concept. One possible limitation to this approach that deserves consideration is as follows. If Mt serves primarily as a sink for otherwise toxic forms of cadmium, then attention should be paid not to the total cadmium content of tissues but rather to the non-Mt fraction (e.g., Nomiyama & Nomiyama 1982). Fractionation of rat jejunal mucosa, for instance, clearly shows that only a portion of the total cadmium is present in the cytosol (Kello et al. 1979); the rest is bound to particulate fractions. Of the cytosolic cadmium a major portion was recovered in the Mt fraction but a significant amount was present also as non-Mt cadmium. A possible limitation is that a critical level of cadmium defined for the renal cortex (see Section VI.B.1) may be valid only for populations in which the same distribution of cadmium among different tissue pools may be assumed. The ways in which various factors (i.e., rate of exposure, age and ambient temperature) affect this distribution have not been fully explored.

G. Summary

The recommended values for the one-day and ten-day HAs for both adults and children, and the AADI are summarized in Table VIII-3.

Table VIII-3 Summary of Quantification of Toxicological Effects

	Cadmium Drinking Water Concentration, mg/L		
	10-kg Child	70-kg Adult	Reference[a]
One-Day Health Advisory	0.043	0.15	Lauwerys (1979)
Ten-Day Health Advisory	0.008	0.029	Kotsonis and Klaassen (1978)
AADI (100% from Drinking Water)	--[b]	0.018	Friberg et al. (1974) Kjellstrom et al. (1984)

[a] Reference used in calculating HA or AADI values.

[b] Not calculated because the AADI is based on life-time exposure.

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